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John Nielsen

PATENT- OG VAREMÆRKESTYRELSEN

DIAMINO-FUNCTIONAL CHALCONES

FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues and to their use as pharmaceutically active agents, in particular against bacterial and parasitic infections

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism selected from *Helicobacter pylori* and *Plasmodium falciparum* The prediction is based on the ability of the chemical compound to act as an inhibitior of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells

BACKGROUND OF THE INVENTION

Chalcones, e g , for use against parasitic infections are known from earlier patent applications assigned to the applicant, e g WO 93/17671 and WO 99/00114

The bioavailability for several of the known chalcones is low due to the low solubility of the compounds The compounds do not typically dissolve in the intestine and are therefore not available for absorption

The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β-lactam-antibiotics and Enterococci resistant to vancomycin (VRE) Such resistant bacteria pose a significant therapeutic challenge and bacterial strains resistant to all currently available antimicrobials are emerging Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients An example of this is *Stenotrophomonas maltophilia* which possesses a β-lactamase rendering the bacteria intrinsically resistant to carbapenems As cross-resistance within a given class of antibiotics often occurs the development of new classes of antibiotics is a neccisity to counter the emerging threat of bacterial resistance

Thus, there is a need for improved chalcone derivatives for therapeutic or prophylactic use against parasites and bacteria

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of diamino-functional chalcones where the aromatic rings are phenyl rings R^4= H (yielding the B ring) or CH_3 (yielding the A ring), R^1, R^2, R^3 and Z are as defined herein

Figure 2 illustrates the scheme for the preparation of diamino (aminoacylamino)-functional chalcones where the aromatic rings are phenyl R^1, R^2 and R^3 are as defined herein, R_4= H or CH_3, and $Y=(C(R^H)_2)_{n\ 1}$

Figure 3 illustrates the synthesis of diamino-dihydrochalcones R^1, R^2, R^3 and Z are as defined herein

Figure 4 illustrates a time-kill curve of I-031 against S aureus ATCC29213 Bacterial growth is inhibited at concentrations at or above the MIC (MIC=37 5 μM) As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound

Figure 5 illustrates a time-kill curve of I-070 against S aureus ATCC29213 Bacterial growth is inhibited at concentrations of test compound at or above the MIC (MIC=9 4 μM) As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal The rate of reduction of CFU/ml is not significantly affected by increasing concentrations of test compound Thus, the bactericidal action of the compound is primarily dependent on incubation time

Figure 6 illustrates a dose-respons curve of LicA and one of the novel diamino-chalcones (I-103) at *Plasmodium falciparum* As shown at the figure, I-103 is 10 times more potent than LicA

DESCRIPTION OF THE INVENTION

The present inventors have found that the diamino-functional chalcone defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents

It is believed that the diamino group or groups of the diamino-functional chalcone will be charged according to pH of the medium and the pKa of the compound The solubility of the charged compounds is many times higher than the solubility of the neutral compounds As the diamino-functional chalcones will be partially charged (i e soluble) at the pH in the intestine, they will dissolve in the gastric juices and be available for absorption The bioavailability of the diamino-functional chalcones will therefore be improved many times compared to the known neutral chalcones making the compounds generally useful as drug candidates Also, the diamino-functional chalcones have different pKa values which enable the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value

The usefulness of the known chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* The inventors have now found that introduction of a diamino group in the chalcone derivative changes the metabolic properties and the compounds prepared show improved metabolic stability

Futhermore, the inventors have found that the diamino-functional chalcones defined herein exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains

Thus, the present invention provides chalcone derivatives and analogues as defined in claim 1, i e a compound of the general formula

$$Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}V\text{-}Ar^2(X^2)Y^2$$

wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

V designates $-CH_2-CH_2-$, -CH=CH- or -C≡C-, preferably -CH=CH-,

one or both of Y^1 and Y^2 independently represent at least one, such as 1-2, e g one, diamino-functional substituent(s) of the formula

$$-NR^3\text{-}Z\text{-}N(R^1)R^2$$

wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each R^H is independently selected from hydrogen and $C_{1\ 6}$-alkyl, or two R^H on the same carbon atom may designate =O,

R^1 and R^2 independently are selected from hydrogen, optionally substituted $C_{1\ 12}$-alkyl, optionally substituted $C_{2\ 12}$-alkenyl, optionally substituted $C_{4\ 12}$-alkadienyl, optionally substituted $C_{6\ 12}$-alkatrienyl, optionally substituted $C_{2\ 12}$-alkynyl, optionally substituted $C_{1\ 12}$-alkoxycarbonyl, optionally substituted $C_{1\text{-}12}$-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)aminocarbonyl, amino-$C_{1\ 6}$-alkyl-aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)amino-$C_{1\ 6}$-alkyl-aminocarbonyl, or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring,
R^3 is selected from hydrogen, $C_{1\ 6}$-alkyl, and $C_{1\ 6}$-alkylcarbonyl, said alkyl and alkylcarbonyl optionally carrying substituent(s) selected from halogen, hydroxy, $C_{1\ 6}$-alkoxy, carboxy, $C_{1\ 6}$-alkoxycarbonyl, $C_{1\ 6}$-alkylcarbonyl, amino, mono- and di($C_{1\ 6}$-alkyl)amino, and aryl optionally substituted 1-3 times with $C_{1\ 4}$-alkyl, $C_{1\ 4}$-alkoxy, nitro, cyano, amino or halogen, or R^1 and R^3 together form a biradical Z^* which is as defined for Z,

X^1 and X^2 independently designates 0-5, preferably 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl-oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine,

and salts thereof

The substituents R^1 and R^2 carried by the one nitrogen atom of the diamino substituent, and R^3 carried by the other nitrogen atom of the diamino substituent are believed to slightly alter the pKa value of the chalcone derivative Thus, the particular selection of the groups R^1, R^2 and R^3 can be used to "fine-tune" the pKa value in view of the particular condition or disease and the intended route of administration

In one embodiment, R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, amino-carbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl In particular R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6}-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl

In another embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached (-$N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring

In a further embodiment, R^3 is selected from hydrogen and methyl, in particular methyl

The selection of the substituents X^1 and X^2 is not very critical Thus, it is believed that these substituents can be chosen fairly freely

However, in still a further embodiment, X^1 and X^2 independently designates 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy-carbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, guanidino, carbamido, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, optionally substituted C_{1-6}-alkylthio, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen, in particular X^1 and X^2 independently designates 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroaryl-sulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclyl-amino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen

The group V is relevant with respect to the spatial orientation of the rings Ar^1 and Ar^2 Thus, the group V may be $-CH_2-CH_2-$, -CH=CH- or -C≡C- Preliminary results have showns that the embodiments wherein V designates -CH=CH- yields valuable chalcone derivatives

The expression "chalcone derivative" has been assigned to the compounds of the above formula in that the overall structure namely Ar^1-C(=O)-C-C-Ar^2 resembles that of the chalcone structure This being said, Ar^1 and Ar^2 are selected from aromatic rings and heteroaromatic rings It is currently believed that particularly interesting compounds are those where at least one of Ar^1 and Ar^2, preferably both, are aromatic rings, in particular phenyl rings This being said, the inventors envisage that the functionality of the

compounds may be substantially preserved (or even improved) when one or both of Ar^1 and Ar^2 are heteroaromatic rings

In one embodiment, at least one or Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl

In another embodiment, both of Ar^1 and Ar^2 are phenyl rings and Y^1 represent at least one diamino-functional substituent

In a further embodiment, X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular, X^2 represents at least two halogen atoms

The Z group represents the biradical between the two nitrogen atoms of the diamino functionality This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, where each R^H is independently selected from hydrogen and C_{1-6}-alkyl, or two R^H on the same carbon atom may designate =O A particular example of Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3

Thus, in a particular embodiment, one of Y^1 and Y^2 represent a substituent of the formula

$$-NR^3-(CH_2)_{2-3}-N(R^1)R^2$$

wherein R^3 is selected from hydrogen and methyl, R^1 and R^2 is selected from hydrogen and C_{1-6}-alkyl Furthermore, V is preferably -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings

In a further embodiment, one of Y^1 and Y^2 represents a substituent of the formula

$$-NR^3-C(=O)-(CH_2)_{1-4}-N(R^1)R^2$$

wherein R^3 is selected from hydrogen and methyl, R^1 and R^2 is selected from hydrogen and C_{1-6}-alkyl Furthermore, V is preferably -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings

Definitions

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compund, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test

compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time

In the present contest, the term "antiparasitic" is intended to describe the ability of a test compound to upon incubation in vitro with a culture of parasites, e g *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures

In the present context, the term "C_{1-12}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc Analogously, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C_{1-4}-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e g methyl, ethyl, propyl, *iso* propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl

Whenever the term "C_{1-12}-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C_{1-6}-alkyl"

Similarly, the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", and "C_{6-12}-alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl

Similarly, the term "C_{2-12}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl

Whenever the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", "C_{6-12}-alkatrienyl", and "C_{2-12}-alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms

In the present context, i e in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the

group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i e C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine

Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i e C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl"

Especially preferred examples are hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, and guanidine

"Halogen" includes fluoro, chloro, bromo, and iodo

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e g nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thiophenyl, quinolyl,

benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thiophenyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiophenyl, quinolyl, tetrazolyl, and isoquinolyl

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e g nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane The most interesting examples are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane

In the present context, i e in connection with the terms "aryl", "heteroaryl", and heterocyclyl, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)-amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine

Preferably, the substituents are selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkylsulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine Especially preferred examples are C_{1-6}-alkyl, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine

In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present Such a nitrogen is, with reference to the formula, carrying the substituents R_1 and R_2 The heterocyclic ring or ring system is a ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e g nitrogen (=N- or -N-), sulphur, and/or oxygen atoms Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxozole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole The most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole

Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, and thiazetane The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane

In the present context, i e in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with

group(s) selected from the same substituents as defined above for "optionally substituted aryl"

As it will be evident from the formulae defined herein and the definitions associated therewith, there may be one or several asymmetric carbon atoms present in the compounds depending on the nature of the substituents The compounds are intended to include all stereoisomers arising from the presence of any and all isomers as well as mixtures thereof, including racemic mixtures

It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications Salts include acid addition salts and basic salts Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^{+}N(R')_4$, where the R"s independently designates optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl) Pharmaceutically acceptable salts are, e g , those described in Remington's - The Science and Practice of Pharmacy, 20th Ed Alfonso R Gennaro (Ed), Lippincott, Williams & Wilkins, ISBN 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology

Thus, chalcones with diamino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations The use of appropriate selected salt form can be used to control the dissolution rate in vivo Furthermore, the different salt forms have different bulk-properties which is of importance for the manufacturing process

Preparation of compounds

The diamino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following Further examples of methods for the preparation of the compound used according to the present invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein

Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a ketone (an acetophenone in the case where Ar^1 is phenyl)

$$Y^1(X^1)\text{-}Ar^1\ C(=O)\text{-}CH_3$$

with an aldehyde (a benzaldehyde in the case where Ar^2 is phenyl)

$$HCO\text{-}Ar^2\text{-}(X^2)Y^2$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, and Y^2 refers to the definitions given elsewhere herein

This reaction, which is a condensation reaction, is suitably carried out under acid or base catalysed conditions A review of such processes may be found in Nielsen, A T , Houlihahn, W J , *Org React* **16**, 1968, p 1-444 In particular the method described by Wattanasin, S and Murphy, S , *Synthesis* (1980) 647 has been found quite successful The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e g methanol, ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic acid), or in aprotic organic solvents such as ethers (e g tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e g dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e g toluene or benzene), or mixtures of such solvents When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum, ammonium, or quaternary ammonium hydroxides, lower alkoxides (e g methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e g diisopropyl amides or methylphenyl amides) Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3, $POCl_3$, PCl_5, or $FeCl_3$), or acid ion exchange resins

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy groups This drawback can be overcome by masking the phenolic group as described by T Hidetsugu et al in EP 0 370 461 Deprotection is easily performed by mineral acids such as hydrochloric acid

The reaction is typically carried out at temperatures in the range of 0-100°C, e g at room temperature Reaction times are typically from 30 min to 24 hours

The starting materials for the synthesis (acetophenone and aldehyde), may be obtained from commercial sources or may be synthesised according to well-known methods The diamino-benzaldehydes can be synthesized by Palladium catalysed reaction of bromo-benzaldehyde diethyl acetal and diamine followed by acidic work up Alternatively, the 2-diamino-benzaldehydes can be prepared by nucleophilic aromatic substitution using 2-fluorobenzaldehyde and diamine The diamino-acetophenones can be synthesized by

Palladium catalysed reaction of bromoacetophenone ketal and diamine followed by acidic work up Alternatively the 2'-diamino-acetophenones can be synthesized by nucleophilic aromatic substitution using 2'-flouroacetophenone and diamine

Compounds of the general formula I in which V is -C≡C- may be prepared by reacting an activated derivative of a carboxylic acid of the general formula

$$Y^1(X^1)\text{-}Ar^1\text{-}COOH$$

with an ethyne derivative

$$H\text{-}C{\equiv}C\text{-}Ar^2\text{-}(X^2)Y^2$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, and Y^2 refers to the definitions given elsewhere herein

Reactions of this type are described by Tohda, Y , Sonogashihara, K , Haghara, N , *Synthesis* **1977**, p 777-778 It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride The reaction is normally carried out using the catalysts described by Tohda, Y *et al* cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride The reaction is suitably carried out in triethylamine, a mixture of triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30 minutes to 6 hours

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions Such protection may be carried out in a well-known manner, e g as described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-Interscience, ISBN 0471160199, 3nd edition (May 15, 1999) For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar^1 and/or Ar^2 may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether The protecting group may be removed after the reaction in a manner known *per se*

The ethyne derivative may be prepared by standard methods, e g as described by Nielsen, S F Et al , Bioorg Med Chem 6, pp 937-945 (1998) The carboxylic acids may likewise be prepared by standard procedures, e g as described by Nakayama, T Chem Pharm Bull 41, pp 117-125 (1993)

Compounds of the general formula I in which V is $-CH_2-CH_2-$ can be prepared by ionic hydrogenation of the corresponding α,β-unsaturated compound where V is -CH=CH- as it has been described by the inventors in Nielsen, S F et al Tetrahedron, 53, pp 5573-5580

(1997) Alternatively, it is possible to prepare such compounds from the corresponding flouro (or bromo) chalcones using H_2/Pt followed by nucleophilic aromatic amination (see Figure 3)

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed (especially chapter 15, pages 691-700) and references cited therein Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones

Medical uses

It has been demonstrated herein (see the Examples section) that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents It is of course possible that the compounds also have other interesting properties to be utilised in the medical field

Thus, the present invention provides a compound (chalcone derivative) as defined herein for use as a drug substance

In particular, the chalcone derivative may be used for the treatment of bacterial infections in a mammal in need thereof Such bacterial infection may be caused by common Gram-positive and Gram-negative pathogens as well as microaerophilic and anaerobic bacteria As a particularly relevant example of a bacteria against which chalcone derivatives have effect can be mentioned antibiotic-sensitive and -resistant strains of *S aureus* and *E faecium* Other examples common causes of community acquired and nosocomial respiratory infections including *S pneumoniae*, *S pyogenes* and members of *Enterobacteriaceae* (e g *E coli*), microaerophilic bacteria associated with gastric disease (e g *Helicobacter pylori*) and pathogenic anaerobic bacteria (e g *Bacteroides fragilis* and *Clostridium species*)

Also, the chalcone derivatives can be used for the treatment of infections caused by protozoa in a mammal Examples of infections are those caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*

Furthermore, the chalcone derivatives can be used for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp* Such infections may be cutaneous and/or visceral

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance

Formulation of pharmaceutical compositions

The administration route of the compounds (diamino-functional chalcones) as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic concentration Thus, e g , the following administration routes may be applicable although the invention is not limited thereto the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route It should be clear to a person skilled in the art that the administration route is dependant on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by weight of the total weight of the composition The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route Thus, the composition may be in form of, e g , tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e g , "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J & J C Boylan, Marcel Dekker, Inc , New York, 1988 Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or exipient Pharmaceutically acceptable carriers or exipients are those known by the person skilled in the art

Thus, the present invention provides a pharmaceutical composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration The latter type of compositions are generally known as controlled release formulations

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of

the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e g , spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations

Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No WO 99/00114, page 29, line 9, to page 40, line 3 Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation Specific formulations can be found in "Remington's Pharmaceutical Sciences"

Dosages

The compound are preferably administered in an amount of about 0 1-50 mg per kg body weight per day, such as about 0 5-25 mg per kg body weight per day

For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated

The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks

The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months, in particular, the treatment of tuberculosis will normally be carried out for 6-12 months

The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure

For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i e from approximately 1 mg to 100 mg per kg body weight per day

For parenteral administration, a dose of about 0 1 mg to about 50 mg per kg body weight per day is convenient For intravenous administration a dose of about 0 1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient For intraarticular administration a dose of about 0 1 mg to about 20 mg per kg body weight per day is usually preferable For parenteral administration in general, a solution in an aqueous medium of 0 5-2% or more of the active ingredients may be employed

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable

In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs Important aspects of this is the use of the compound against Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another antimalarial drug

Method of prediction

In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B

The method can be performed as described under *DHODH Assay* in the Examples section It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any

compound Preferably, however, the chemical compound is a chalcone derivative, e g a chalcone derivative as defined herein

EXAMPLES

Preparation of compounds

The general method for the preparation of the A ring or B ring having the diamino-functional group is illustrated in Figure 1

General procedure A

Amination of bromobenzaldehydes

Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), $Pd_2(dba)_3$ (0 2 mmol, 1 mol% Pd), *rac*-BINAP (0 6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The solution was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL) The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using 5% Et_3N in EtOAc

General procedure B

Nucleophilic aromatic substitution on Fluorobenzaldehyde

A stirred solution of fluoro-benzaldehyde (49 3 mmol) in dry DMF (50 mL) was added K_2CO_3 (10 2 g, 74 0 mmol) and amine (74 mmol) and left overnight at 100°C The reaction mixture was cooled to room temperature, added water (100 mL) and extracted with ether (3 x 50 mL) The combined organic phases was washed with water and dried (Na_2SO_4) Evaporation *in vacuo* and recrystallization (heptane) gave the product

General Procedure C

Amination of bromoacetophenones

3'- or 4'-bromoacetophenone was converted into the corresponding cyclic ketal A solution of 3- or 4-bromoacetophenone (0 10 mol), 1,3-propandiol (0 12 mol) and p-TsOH (0 1 g) in toluene (200 mL) was heated and water was azeotropically removed using a Dean-Stark water-separator After 18 hours, the solution was washed with 5% Na_2CO_3 (100 ml), dried (K_2CO_3) and the solvent was removed under reduced pressure According to ^{1}HNMR the ketals was pure enough for further reaction

3'- or 4'-bromoacetophenone ketal (40 mmol), amine (48 mmol), $Pd_2(dba)_3$ (0 2 mmol, 1 mol% Pd), *rac*-BINAP (0 6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The solution was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL) The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using 5% Et_3N in EtOAc

General procedure D

Nucleophilic aromatic substitution on Fluoroacetophenone

A mixture of Fluoroacetophenone (40 mmol), amine (50 mmol), K_2CO_3 (50 mmol) was refluxed in dry DMF (20 mL) under an argon atmosphere for 18 h The DMF was removed using an oilpump and water (50 mL) was added to the residue The water phase was extracted with Et_2O (2 x 100 mL) and the organic phase was dried (K_2CO_3) and evaporated to yellow oil, which was pure enough for further reaction

General procedure E

Preparation of alkyl aminomethyl acetophenones

To a solution of (2-methyl-[1,3]dioxan-2-yl) benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1 5 L) was added sodium triacetoxyborohydride (257mmol) under argon The resulting suspension was stirred at room temperature for 18 hr A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M) The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded The pH of the aqueous phase was adjusted to 11 - 14 using sodium hydroxide and extracted again with diethyl ether The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification

General procedure F

Preparation of alkyl aminomethyl benzaldehydes

To a solution of diethoxymethyl benzaldehyde (16 5 mmol) and amine (24 7 mmol) in dry THF (150 mL) was added sodium triacetoxyborohydride (25 7mmol) under argon The resulting suspension was stirred at room temperature for 6-18 hr A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M) The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded The pH of the aqueous phase was adjusted to 11 - 14

using sodium hydroxide and extracted again with diethyl ether The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification

General procedure G

Preparation of (2-dimethylaminoethoxy)-benzaldehydes

A stirred solution of hydroxybenzaldehyde (59 7 mmol) in dry toluene (200 mL) and DMSO (1 mL) was added 60% NaH (60 mmol) under ice cooling The reaction was slowly heated to room temperature 2-Dimethylaminoethylchloride, HCl (15 9 g, 110 mmol) dissolved in water (50 mL) was added NaOH (4 4 g, 110 mmol) and the aqueous phase was extracted with toluene (3 x 30 mL) The combined organic phases were dried (Na_2SO_4) and slowly added to the reaction The solution was heated to 90°C for 16 h The reaction mixture was cooled to room temperature and washed with water (3 x 100 mL), 2N NaOH (100 mL) and dried (Na_2SO_4) Evaporation *in vacuo* gave the title products

General procedure H

Preparation of biaryl carbaldehydes

A solution of Na_2CO_3 (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14 7 mmol) and (hetero)arylboronic acid (17 6 mmol) in DME (40 mL) The mixture was flushed with argon for 2 minutes followed by addition of $Pd(PPh_3)_2Cl_2$ (310 mg, 3 mol %) The reaction was heated at reflux and left overnight under an atmosphere of argon The reaction was cooled, 2M Na_2CO_3 was added, and the mixture was extracted with EtOAc (3 x 20 mL) The title products were purified by flash chromatography

General procedure I

Amino-acylation of amino-acetophenones and amino-benzaldehydes

A solution of amino-acetophenone/benzaldehyde (25 mmol) in THF (100 mL) was added chloroacyl chloride (30 mmol) The mixture was stirred for 30 min, poured into icecold 2M NaOH (aq) and extracted with Et_2O The organic phase was dried and the solvent was removed under reduced pressure giving the pure product A solution of the product (10 mmol) and triethyl amine (30 mmol) in ethanol was added amine (20 mmol) and the mixture was refluxed for 4 hours Ethanol was removed under reduced pressure and the product was dissolved in EtOAc and washed with 2M NaOH (aq) EtOAc was removed under reduced pressure giving the product as a pure oil

General procedure J

Synthesis of (amino-)chalcones

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added 8M NaOH (0 3 mL), and the mixture was stirred for 3-18 hours at 25°C The mixture was evaporated on Celite® and the product was isolated by flash chromatography The aminochalcone was dissolved in MeOH Et_2O (1 9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH Et_2O (1 9 v/v) was added The salt was filtered off and recrystallised from MeOH or MeCN Some aminochalcones did not undergo saltformation, and was isolated as the free base The purity was >95% determined by HPLC and the molecular weight was determined by LC-MS

General procedure K

Synthesis of (hetero)aryl chalcones from bromo-chalcones

A solution of bromo-chalcone (0 92 mmol) and (hetero)aryl boronic acid (1 11 mmol) in DME (10 mL) was added a solution of Na_2CO_3 (290 mg, 2 8 mmol) in water (5 mL) The mixture was bubbled through with argon for 2 minutes followed by addition of $Pd(PPh_3)_2Cl_2$ (19 mg, 3 mol %) The reaction was heated to reflux and left overnight under an atmosphere of argon The solution was cooled, added 2M Na_2CO_3, extracted with ether (3 x 20 mL) and purified by column chromatography

General procedure L

Synthesis of fluoro-(or bromo-)dihydrochalcones

Fluoro- (or bromo-)chalcone was dissolved in EtOAc (100 mL), and 5% Pt/C (100 mg) was added and the mixture was hydrogenated at 1 bar H_2 The addition of hydrogen was stopped when the theoretical amount was absorbed (1 eqv H_2) The mixture was filtered and evaporated leaving the product as an oil The product was purified by column chromatography or crystallisation

General procedure M

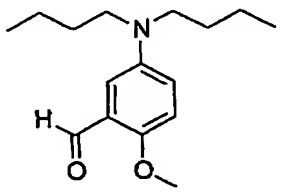
Synthesis of fluoro- (or bromo)-diamino-dihydrochalcones

A mixture of fluoro-dihydrochalcone (4 5 mmol), amine (6 0 mmol), K_2CO_3 (0 83 g, 6 0 mmol) was refluxed in dry degassed DMF (6 mL) for 24 h The red mixture was poured into water (100 mL) and extracted with EtOAc (3 x 30 mL), dried (K_2CO_3) and the solvent was removed under reduced pressure The resulting dark oil was purified by column chromatography (SiO_2) using EtOAc as eluent

5-Dibutylamino-2-methoxy-benzaldehyde

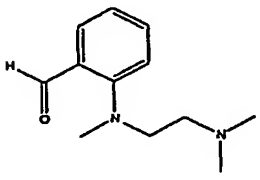
I-001 2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane
A solution of 5-bromo-*o*-anisaldehyde (25 g, 116 mmol), 1,3-propandiol (9 mL, 125 mmol), *p*-toluenesulphonic acid (0 1 g) in toluene (150 mL) was heated and water was azeotropically removed using a Dean-Stark water-separator After 18 hours, the solution was washed with 5% Na_2CO_3 (100 ml), dried (K_2CO_3) and the solvent was removed under reduced pressure The acetal was purified by vacuumdistillation and isolated as an clear oil bp 126-130°C/0 05 mbar
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 74 (d, 1H), 7 38 (dd, 1H), 6 75 (d, 1H), 5 82 (s, 1H), 4 28-4 20 (m, 2H), 4 04-3 92 (m, 2H), 3 80 (s, 3H), 2 33-2 13 (m, 1H), 1 48-1 38 (m, 1H)

I-002 5-Dibutylamino-2-methoxy-benzaldehyde
2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane (40 mmol), di-*n*-butylamine (48 mmol), $Pd_2(dba)_3$ (0 2 mmol, 1 mol% Pd), P(*o*-tol)$_3$ (0 6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The solution was cooled to 0°C and pH was adjusted to 9 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL) The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using EtOAc/*n*-heptane (1 4, v/v) as eluent The product was isolated as a yellow oil in 46% yield



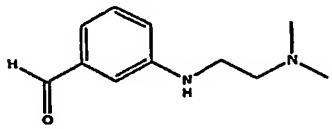
^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 98 (s, 1H), 7 15 (d, 1H), 6 92 (d, 1H), 6 79 (dd, 1H), 3 80 (s, 3H), 3 25 (t, 4H), 1 55-1 40 (m, 4H), 1 40-1 25 (m, 4H), 0 91 (t, 6H)

I-003 2-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde



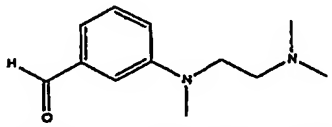
General procedure B gave the title compound as a yellow oil in 56% yield ref 1
^{1}H-NMR(300 MHz, $CDCl_3$) δ 10 29 (s, 1H), 7 82-7 75 (dd, 1H), 7 53-7 43 (td, 1H), 7 13 (d, 1H), 7 05 (t, 1H), 3 25 (t, 2H), 2 92 (s, 3H), 2 52 (t, 2H), 2 22 (s, 6H)

I-004 3-(2-Dimethylamino-ethylamino)benzaldehyde



General procedure A gave the title compound as a yellow oil in 52% yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 81 (s, 1H), 7 65 (d, 2H), 6 60 (d, 2H), 5 11 (s, br, 1H), 3 20-3 14 (m, 2H), 2 56 (t, 2H), 2 26 (s, 6H)

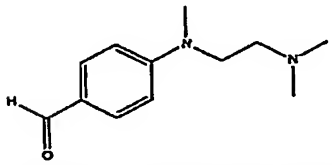
I-005 3-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde



General procedure A gave the title compound as a yellow oil in 90% yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 91 (s, 1H), 7 35 (t, 1H), 7 12-7 05 (m, 2H), 7 00-6 93 (dd, 1H), 3 56 (t, 2H), 3 05 (s, 3H), 2 55 (t, 2H), 2 38 (s, 6H)

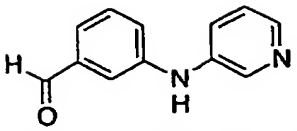
I-006 4-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde



General procedure A gave the title compound as a yellow oil in 66% yield ref 2

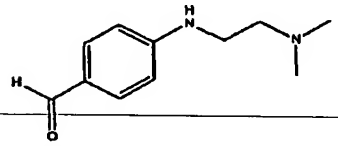
^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 73 (s, 1H), 7 73 (d, 2H), 6 71 (d, 2H), 3 54 (t, 2H), 3 08 (s, 3H), 2 50 (t, 2H), 2 30 (s, 6H)

I-007 3-(Pyridin-3-ylamino)-benzaldehyde



General procedure A gave the title compound as white crystal in 69& yield
^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 94 (s, 1H), 8 67 (s, 1H), 8 40 (d, 1H), 8 11 (dd, 1H), 7 58-7 50 (m, 2H), 7 47 (d, 1H), 7 43-7 35 (m, 2H), 7 29 (dd, 1H)

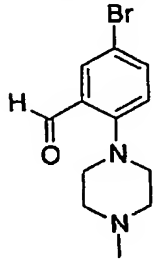
I-008 4-(2-Dimethylamino-ethylamino) benzaldehyde



General procedure A gave the title compound as a yellow oil in 74% yield ref 2

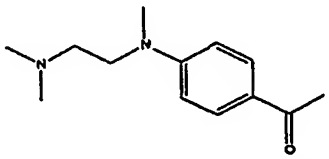
^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 71 (s, 1H), 7 68 (d, 2H), 6 61 (d, 2H), 5 08 (s, br, 1H), 3 24-3 18 (m, 2H), 2 57 (t, 2H), 2 26 (s, 6H)

I-009 5-Bromo-2-(4-methyl-piperazin-1-yl)-benzaldehyde



General procedure B gave the title compound as yellow crystals in 62% yield
^{1}H NMR ($CDCl_3$) δ 10 24 (s, 1H), 7 91 (d, 1H), 7 61 (dd, 1H), 7 02 (d, 1H), 3 11 (t, 4H), 2 63 (t, 4H), 2 39 (s, 3H)

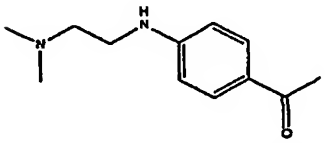
I-010 1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone



General procedure C gave the title compound as an yellow oil in 62% yield ref 3

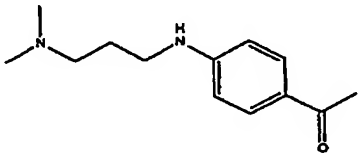
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 72 (d, 2H), 6 73 (d, 2H), 3 53 (t, 2H), 3 08 (s, 3H), 2 50 (t, 2H), 2 48 (s, 3H), 2 30 (s, 6H)

I-011 1-[4-(2-Dimethylamino-ethylamino)-phenyl]ethanone



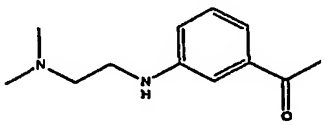
General procedure C gave the title compound as a yellow oil in 92% yield ref 3
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 80 (d, 2H), 6 54 (d, 2H), 5 29 (s, br, 1H), 3 33-3 24 (m, 2H), 2 57 (t, 2H), 2 56 (s, 3H), 2 31 (s, 6H)

I-012 1-[4-(3-Dimethylamino-propylamino)-phenyl]ethanone



General procedure C gave the title compound as a yellow oil in 56% yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 81 (d, 2H), 6 54 (d, 2H), 5 31 (s, br, 1H), 3 25 (t, 2H), 2 48 (s, 3H), 2 41 (t, 2H), 2 25 (s, 6H), 1 79 (m, 2H)

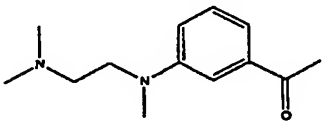
I-013 1-[3-(2-Dimethylamino-ethylamino)-phenyl]ethanone



General procedure C gave the title compound as a yellow oil in 73% yield

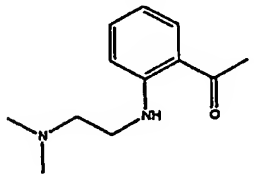
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 28-7 18 (m, 3H), 6 85-6 78 (m, 1H), 4 45 (s, br, 1H), 4 10-3 23 (m, 2H), 2 59-2 52 (m, 5H), 2 25 (s, 6H)

I-014 1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone



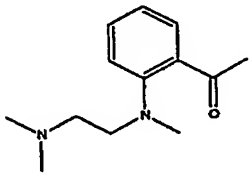
General procedure C gave the title compound as a yellow oil in 62% yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 30-7 18 (m, 3H), 6 82-6 78 (m, 1H), 3 56 (t, 2H), 3 05 (s, 3H), 2 55 (t, 2H), 2 48 (s, 3H), 2 38 (s, 6H)

I-015 1-[2-(2-Dimethylamino-ethylamino)-phenyl]ethanone



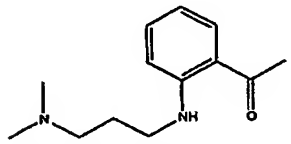
General procedure D gave the title compound as a yellow oil in 58% yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 95 (s, br, 1H), 7 76-7 71 (dd, 1H), 7 38-7 31 (d, 1H), 6 73-6 66 (d, 1H), 6 61-6 55 (td, 1H), 3 33-3 24 (m, 2H), 2 58 (t, 2H), 2 56 (s, 3H), 2 30 (s, 6H)

I-016 1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone



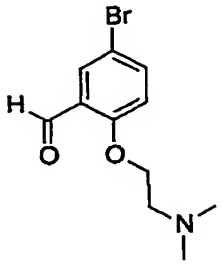
General procedure D gave the title compound as a yellow oil in 93 % yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 42-7 32 (m, 2H), 7 07 (d, 1H), 7 70-6 93 (td, 1H), 3 17 (t, 2H), 2 80 (s, 3H), 2 61 (s, 3H), 2 49-2 42 (m, 2H), 2 20 (s, 6H)

I-017 1-[2-(3-Dimethylamino-propylamino)-phenyl]ethanone



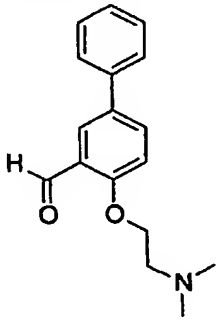
General procedure D gave the title compound as a yellow oil in 45% yield
^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 91 (s, br, 1H), 7 74-7 70 (dd, 1H), 7 38-7 31 (d, 1H), 6 73-6 65 (d, 1H), 6 61-6 55 (td, 1H), 3 25 (t, 2H), 2 48 (s, 3H), 2 41 (t, 2H), 2 25 (s, 6H), 1 79 (m, 2H)

I-018 5-Bromo-2-(2-dimethylamino-ethoxy)-benzaldehyde



General procedure G gave the title compound as a yellow oil in 65 % yield
^{1}H NMR ($CDCl_3$) δ 10 43 (s, 1H), 7 94 (d, 1H), 7 63 (dd, 1H), 6 92 (d, 1H), 4 19 (t, 2H), 2 81 (t, 2H), 2 37 (s, 6H)

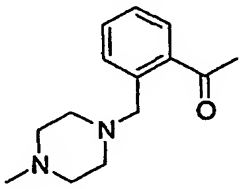
I-019 4-(2-Dimethylamino-ethoxy)-biphenyl-3-carbaldehyde



General procedure H gave the title compound as yellow crystals in 57% yield

^{1}H NMR ($CDCl_3$) δ 10 48 (s, 1H), 8 01 (d, 1H), 7 71 (dd, 1H), 7 49 (d, 1H), 7 36 (t, 2H), 7 26 (t, 1H), 7 00 (d, 1H), 4 18 (t, 2H), 2 77 (t, 2H), 2 31 (s, 6H)

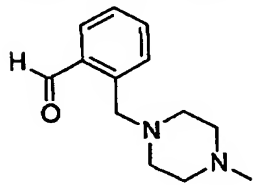
I-020 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone



General procedure E gave the title compound as a brown oil in 78% yield

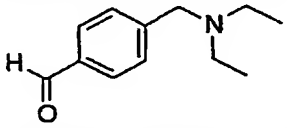
^{1}H-NMR ($CDCl_3$) δ 7 42-7 29 (m, 4H), 3 65 (s, 2H), 2 54 (s, 3H), 2 43 (b, 8H), 2 27 (s, 3H)

I-021 2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde



General procedure F gave the title compound as a brown oil in 80 % yield
^{1}H-NMR(300 MHz, CDCl3) δ 10 41 (s, 1H), 7 87 (d, 1H), 7 51 (dt, 1H)7 41 (t, 1H), 7 38 (d, 1H), 3 81 (s, 2H), 2 6-2 3 (m, 8H), 2 27 (s, 3H)

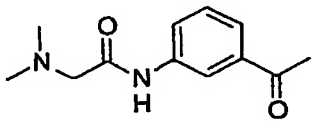
I-022 4-Diethylaminomethyl-benzaldehyde



General procedure F gave the title compound as a brown oil in 74% yield

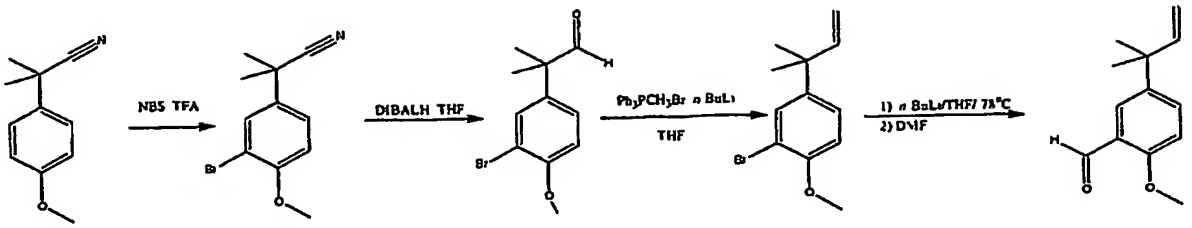
^{1}H-NMR ($CDCl_3$) δ 10 02 (s, 1H), 7 85 (d, 2H), 7 55 (d, 2H), 3 66 (s, 2H), 2 56 (k, 4H), 1 07 (t, 6H)

I-023 N-(3-Acetyl-phenyl)-2-dimethylamino-acetamide

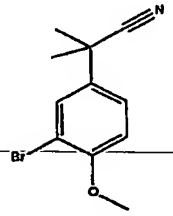


General procedure I gave the title compound as a brown oil in 85% yield
^{1}H-NMR(300 MHz, CDCl3) δ 9 31 (s, 1H), 8 05 (m, 2H), 7 72 (dt, 1H), 7 46 (t, 1H), 3 11 (s, 2H), 2 62 (s, 3H), 2 41 (s, 6H)

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde

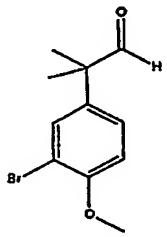


I-024 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile



A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17 5 g, 0 10 mol) in TFA (80 mL) was cooled to 0°C N-bromosuccinimide (17 8 g, 0 10 mol) was added in small portions keeping the temperature below 5°C The orange solution was stirred for 2h/25°C and evaporated to dryness Water (200 mL) was added and the mixture was stirred vigorously for 1 h The crude product was filtered off and recrystallized from boiling MeOH The pure product was isolated as white needles Yield 19 3 g (76%) GCMS > 99% ^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 68 (d, 1H), 7 50 (dd, 1H), 7 16 (d, 1H), 3 86 (s, 3H), 1 70 (s, 6H)

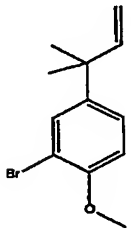
I-025 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde



A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12 71 g, 0 050 mol) in dry THF (100 mL) was cooled to −10°C under argon DIBALH (1M in THF, 100 mL, 0 10 mol) was added keeping the temperature below 0°C The mixture was stirred for 30 min/0°C and then 2 h/25°C The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL) The THF was removed under reduced pressure to give clear oil The oil was destilled (b p 114-130 °C/ 4 3 x 10^{-3} mbar) Yield 7 40 g (58%) GCMS > 99%

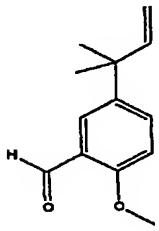
^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 44 (s, 1H), 7 45 (d, 1H), 7 15 (dd, 1H), 6 90 (d, 1H), 3 89 (s, 3H), 1 43 (s, 6H)

I-026 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene



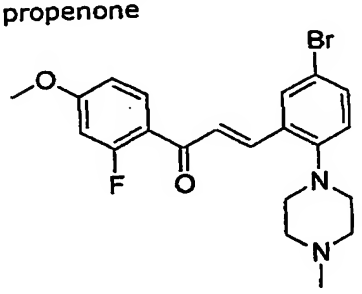
A suspension of methyltriphenylphosphonium bromide (7 71 g, 0 0215 mol) in dry THF (100 mL) was cooled to 0°C under argon *n*-BuLi (2 5M, 8 mL, 0 020 mol) was added slowly The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3 7 g, 0 014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL) The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent Yield 3 1 g (84%) GCMS > 99%
^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 50 (d, 1H), 7 23 (dd, 1H), 6 83 (d, 1H), 5 97 (dd, 1H), 5 06 (dd, 1H), 5 02 (dd, 1H), 3 87 (s, 3H), 1 44 (s, 6H)

I-027 5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde



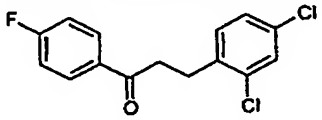
To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3 1 g, 0 012 mol) in dry THF (50 mL) was cooled to -78°C under argon *n*-BuLi (2 5M, 5 1 mL, 0 0128 mol) was added keeping the temperature below -70°C The yellow mixture was stirred for another 15 min and quenched with dry DMF (1 4 mL, 0 018 mol) The cooling bath was removed and the mixture was allowed to warm to 25°C A saturated solution of $NaHCO_3$ (30 mL) was added and then extracted with EtOAc (3 x 50 mL) The organic phase was dried (Na_2SO_4) and evaporated to yellow oil Yield 2 31 g (94%)
^{1}H-NMR(300 MHz, $CDCl_3$) δ 10 48 (s, 1H), 7 84 (d, 1H), 7 55 (dd, 1H), 6 94 (d, 1H), 6 00 (dd, 1H), 5 05 (dd, 1H), 5 01 (dd, 1H), 3 93 (s, 3H), 1 41 (s, 6H)

I-028 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



General procedure J gave the title compound as yellow crystals in 65 % yield
^{1}H NMR ($CDCl_3$) δ 8 05 (dd, 1H), 7 91 (t, 1H), 7 76 (d, 1H), 7 46 (dd, 1H), 7 41 (dd, 1H), 6 96 (dd, 1H), 6 82 (dd, 1H), 6 69 (dd, 1H), 3 90 (s, 3H), 3 01 (t, 4H), 2 64 (bs, 4H), 2 39 (s, 3H)

I-029 3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)propan-1-one



General procedure L gave the title compound as colourless crystals in 53 % yield
^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 12-8 04 (m, 2H), 7 58 (d, 1H), 7 46 (d, 1H), 7 40-7 30 (m, 3H), 3 37 (t, 2H), 3 02 (t, 2H)

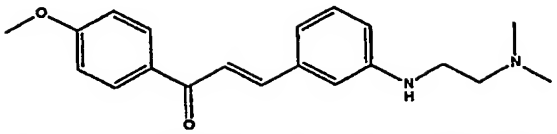
References

1) **Synthesis of 2-phenylthiazolidine derivatives as cardiotonic agents I 2-Phenylthiazolidine-3-thiocarboxamides** Nate, Hiroyuki, Sekine, Yasuo, Honma, Yasushi, Nakai, Hideo, Wada, Hiroshi, Takeda, Mikio, Yabana, Hideo, Nagao, Taku Org Chem Res Lab , Tanabe Seiyaku Co , Ltd , Toda, Japan *Chem Pharm Bull* **(1987)**, *35(5)*, 1953-68

2) **Preparation of stilbenes as neoplasm inhibitors and agents for treating dermatoses**, EP 331983 A2

3) **Preparation of 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidines as adenosine kinase inhibitors**, WO 00/23444 A1

I-030
(*E*)-3-[3-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone

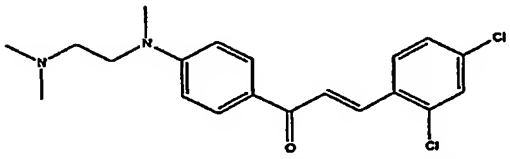


General procedure J gave the fumaric acid salt of title compound as yellow crystals in 64 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 14 (d, 2H), 7 81 (d, 1H), 7 59 (d, 1H), 7 16 (t, 1H), 7 12-7 00 (m, 4H), 6 73-6 68 (dd, 1H), 6 56 (s, 2H), 3 88 (s, 3H), 3 30 (t, 2H), 2 79 (t, 2H), 2 44 (s, 6H)

I-031

(*E*)-3-(2,4-Dichloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

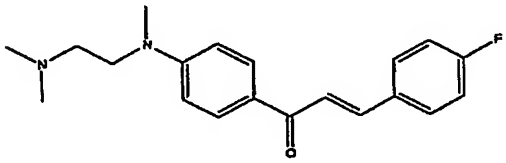


General procedure J gave the oxalate salt of title compound as yellow crystals in 15 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 26 (d, 1H), 8 08 (d, 2H), 8 00 (d, 1H), 7 89 (d, 1H), 7 74 (s, 1H), 7 54 (d, 1H), 6 86 (d, 2H), 3 78 (t, br, 2H), 3 12 (t, br, 2H), 3 07 (s, 3H), 2 75 (s, 6H)

I-032

(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-fluoro-phenyl)-propenone

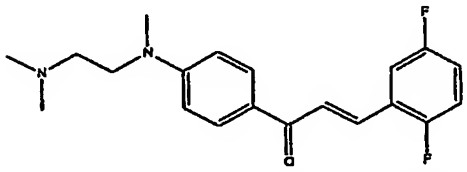


General procedure J gave the oxalate salt of title compound as yellow crystals in 12 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 06 (d, 2H), 7 98-7 82 (m, 3H), 7 65 (d, 1H), 7 28 (t, 2H), 6 86 (d, 2H), 3 80 (t, 3H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

I-033

(*E*)-3-(2,5-Difluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

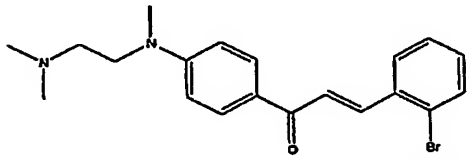


General procedure J gave the oxalate salt of title compound as yellow crystals in 12 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 11 (m, 4H), 7 69 (d, 1H), 7 41-7 28 (m, 2H), 6 86 (d, 2H), 3 80 (t, 3H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

I-034

(*E*)-3-(2-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

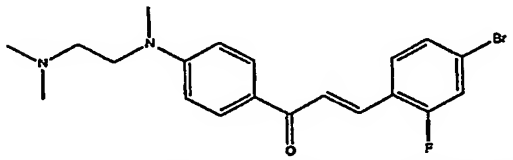


General procedure J gave the oxalate salt of title compound as yellow crystals in 18 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 16 (dd, 1H), 8 07 (d, 2H), 7 92 (s, 2H), 7 73 (dd, 1H), 7 48 (t, 1H), 7 40-7 36 (td, 1H), 6 86 (d, 2H), 3 79 (t, 3H), 3 11 (t, 2H), 3 04 (s, 3H), 2 74 (s, 6H)

I-035

(*E*)-3-(4-Bromo-2-fluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

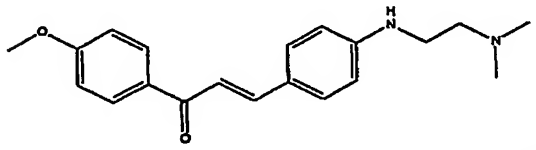


General procedure J gave the oxalate salt of title compound as yellow crystals in 18 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 12-7 96 (m, 4H), 7 72-7 64 (m, 2H), 7 56-7 50 (dd, 1H), 6 86 (d, 2H), 3 78 (t, 3H), 3 08 (t, 2H), 3 04 (s, 3H), 2 74 (s, 6H)

I-036

(*E*)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone

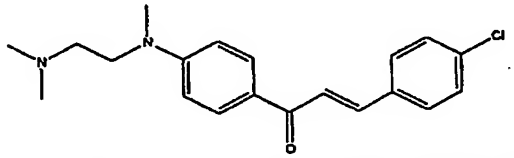


General procedure J gave the fumarate salt of title compound as yellow crystals in 44 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 10 (d, 2H), 7 64-7 58 (m, 4H), 7 05 (d, 2H), 6 65 (d, 2H), 6 58 (d, 2H), 6 38 (s, br, 1H), 3 85 (s, 3H), 2 70 (t, 2H), 2 39(s, 6H)

I-037

(*E*)-3-(4-Chloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

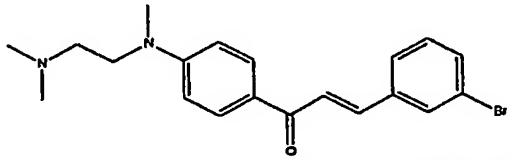


General procedure J gave the oxalate salt of title compound as yellow crystals in 36 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 07 (d, 2H), 7 97-7 87 (m, 3H), 7 63 (d, 1H), 7 51 (d, 2H), 6 84 (d, 2H), 3 74 (t, 2H), 3 48 (t, 2H), 3 05 (s, 3H), 2 70 (s, 6H)

I-038

(*E*)-3-(3-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

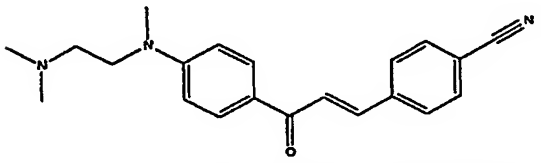


General procedure J gave the oxalate salt of title compound as yellow crystals in 23 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 17 (s, 1H), 8 09 (d, 2H), 7 95 (d, 1H), 7 83 (d, 1H), 7 65-7 55 (m, 2H), 7 40 (t, 1H), 6 85 (d, 2H), 3 80 (t, 2H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

I-039

(*E*)-4-(3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-oxo-propenyl)-benzonitrile

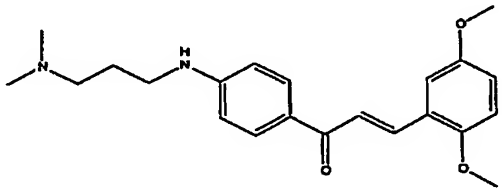


General procedure J gave the oxalate salt of title compound as yellow crystals in 25 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 12-8 03 (m, 4H), 8 02-7 96 (m, 1H), 7 95-7 88 (m, 2H), 7 67 (d, 1H), 6 85 (d, 2H), 3 75 (t, 2H), 3 10-3 02 (m, 5H), 2 70 (s, 6H)

I-040

(*E*)-3-(2,5-Dimethoxy-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone

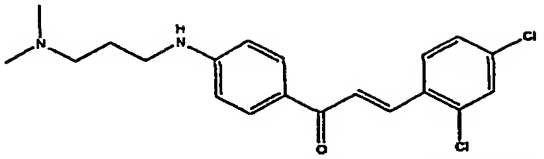


General procedure J gave the oxalate salt of title compound as yellow crystals in 26 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 98 (d, 2H), 7 92 (d, 1H), 7 83 (d, 1H), 7 49 (d, 1H), 7 06-6 97 (m, 2H), 6 75 (s, br, 1H), 6 66 (d, 2H), 3 84 (s, 3H), 3 79 (s, 3H), 3 20 (t, 2H), 3 09 (t, 2H), 2 74 (s, 6H), 1 92 (m, 2H)

I-041

(*E*)-3-(2,4-Dichloro-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone

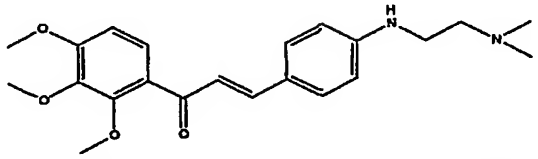


General procedure J gave the oxalate salt of title compound as yellow crystals in 26 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 22 (d, 1H), 8 06-7 92 (m, 3H), 7 86 (d, 1H), 7 72 (d, 1H), 7 52 (dd, 1H), 6 88 (s, br, 1H), 6 67 (d, 2H), 3 22 (t, 2H), 3 10 (t, 2H), 2 74 (s, 6H), 1 93 (m, 2H)

I-042

(*E*)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

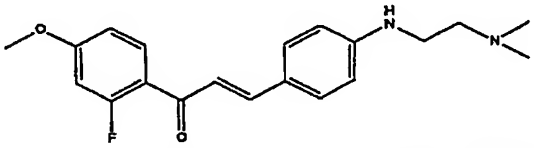


General procedure J gave the fumarate salt of title compound as yellow crystals in 50 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 48 (d, 2H), 7 42 (d, 1H), 7 29 (d, 1H), 7 12 (d, 1H), 6 90 (d, 1H), 6 64 (d, 2H), 6 58 (s, 2H), 6 52 (s, br, 1H), 3 85 (s, 3H), 3 80 (s, 3H), 3 77 (s, 3H), 3 34 (t, 2H), 2 90-2 80 (m, 2H), 2 51 (s, 6H)

I-043

(*E*)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

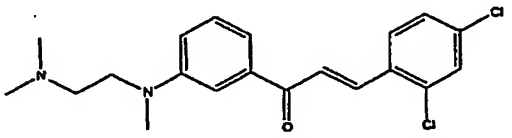


General procedure J gave the fumarate salt of title compound as yellow crystals in 51 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 78 (t, 1H), 7 58-7 48 (m, 3H), 7 16 (dd, 1H), 6 97-6 87 (m, 2H), 6 64 (d, 2H), 6 58 (s, 2H), 6 41 (s, br, 1H), 3 85 (s, 3H), 3 25 (m, 2H), 2 64 (t, 2H), 2 35 (s, 6H)

I-044

(*E*)-3-(2,4-Dichloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

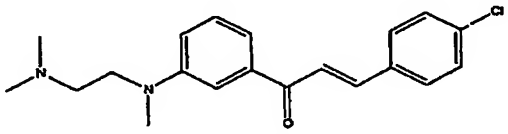


General procedure J gave the oxalate salt of title compound as yellow crystals in 39 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 24 (d, 1H), 7 95 (s, 2H), 7 77 (d, 1H), 7 58-7 50 (m, 2H), 7 44-7 34 (m, 2H), 7 12 (dd, 1H), 3 75 (t, 2H), 3 16 (t, 2H), 3 00 (s, 3H), 2 79 (s, 6H)

I-045

(*E*)-3-(4-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

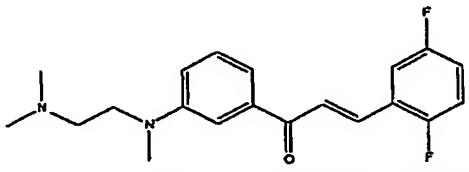


General procedure J gave the oxalate salt of title compound as yellow crystals in 41 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 94-7 87 (m, 3H), 7 70 (d, 1H), 7 54-7 48 (m, 3H), 7 42-7 34 (m, 2H), 7 11 (dd, 1H), 3 76 (t, 2H), 3 18 (t, 2H), 3 00 (s, 3H), 2 80 (s, 6H)

I-046

(*E*)-3-(2,5-Difluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

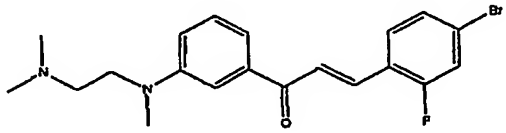


General procedure J gave the oxalate salt of title compound as yellow crystals in 15 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 10-8 04 (m, 1H), 8 00 (d, 1H), 7 75 (d, 1H), 7 53 (d, 1H), 7 44-7 33 (m, 4H), 7 13 (dd, 1H), 3 75 (t, 2H), 3 17 (t, 2H), 3 00 (s, 3H), 2 78 (s, 6H)

I-047

(*E*)-3-(4-Bromo-2-fluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

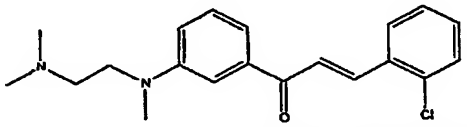


General procedure J gave the oxalate salt of title compound as yellow crystals in 35 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 09 (t, 1H), 7 96 (d, 1H), 7 73 (d, 1H), 7 69 (dd, 1H), 7 54 (dd, 1H), 7 49 (d, 1H), 7 40 (t, 1H), 7 34 (s, br, 1H), 7 12 (dd, 1H), 3 75 (t, 2H), 3 16 (t, 2H), 3 00 (s, 3H), 2 78 (s, 6H)

I-048

(*E*)-3-(2-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

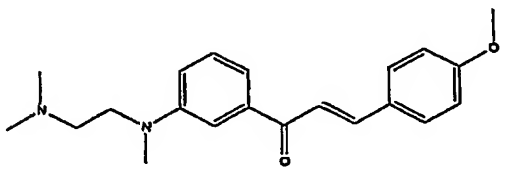


General procedure J gave the oxalate salt of title compound as yellow crystals in 27 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 19 (dd, 1H), 8 02 (d, 1H), 7 92 (d, 1H), 7 57 (dd, 1H), 7 53-7 34 (m, 5H), 7 12 (dd, 1H), 3 75 (t, 2H), 3 15 (t, 2H), 3 00 (s, 3H), 2 78 (s, 6H)

I-049

(*E*)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone

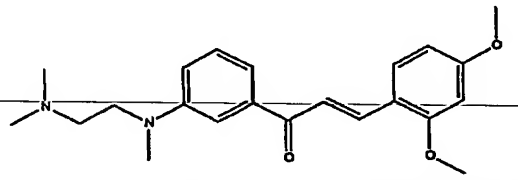


General procedure J gave the oxalate salt of title compound as yellow crystals in 14 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 84 (d, 2H), 7 73 (d, 1H), 7 68 (d, 1H), 7 47 (d, 1H), 7 38 (t, 1H), 7 33 (s, br, 1H), 7 08 (dd, 1H), 7 01 (d, 2H), 3 82 (s, 3H), 3 74 (t, 2H), 3 14 (t, 2H), 2 99 (s, 3H), 2 76 (s, 6H)

I-050

(*E*)-3-(2,4-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

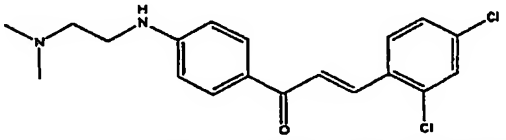


General procedure J gave the oxalate salt of title compound as yellow crystals in 55 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 95 (d, 1H), 7 88 (d, 1H), 7 67 (d, 1H), 7 44-7 32 (m, 2H), 7 30 (s, br, 1H), 7 06 (dd, 1H), 6 66-6 58 (m, 2H), 3 58 (s, 3H), 3 65 (s, 3H), 3 54 (t, 2H), 3 12 (t, 2H), 2 97 (s, 3H), 2 75 (s, 6H)

I-051

(*E*)-3-(2,4-Dichloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

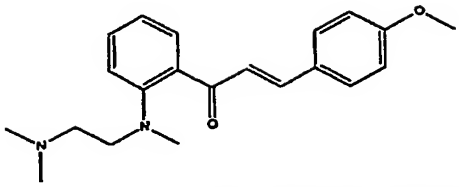


General procedure J gave the fumarate salt of title compound as yellow crystals in 34 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 20 (d, 1H), 8 05-7 91 (m, 3H), 7 86 (d, 1H), 7 71 (d, 1H), 7 50 (dd, 1H), 6 88 (s, br, 1H), 6 67 (d, 2H), 3 80 (t, 2H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

I-052

(*E*)-1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone

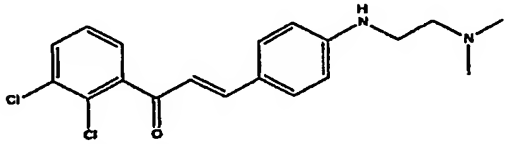


General procedure J gave the oxalate salt of title compound as yellow crystals in 27 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 72 (d, 2H), 7 54-7 38 (m, 3H), 7 25 (d, 1H), 7 19 (d, 1H), 7 08 (t, 1H), 7 00 (d, 2H), 3 82 (s, 3H), 3 38 (t, 2H), 3 18 (t, 2H), 2 73 (s, 6H), 2 70 (s, 3H)

I-053

(*E*)-1-(2,3-Dichloro-phenyl)-3-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

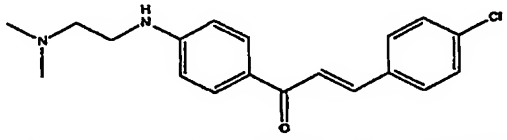


General procedure J gave the fumarate salt of title compound as yellow crystals in 27 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 76 (dd, 1H), 7 52-7 40 (m, 4H), 7 21 (d, 1H), 6 85 (d, 1H), 6 62 (d, 2H), 6 70 (s, 2H), 3 30-3 22 (m, 2H), 2 65 (t, 2H), 2 35 (s, 6H)

I-054

(*E*)-3-(4-Chloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

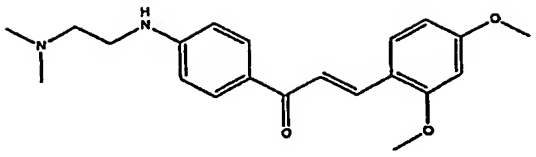


General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 90 (d, 2H), 7 86 (d, 1H), 7 80 (d, 2H), 7 68 (d, 1H), 7 51 (d, 2H), 6 70 (d, 2H), 6 56 (s, 2H), 3 28 (t, 2H), 2 74 (t, 2H), 2 41 (s, 6H)

I-055

(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

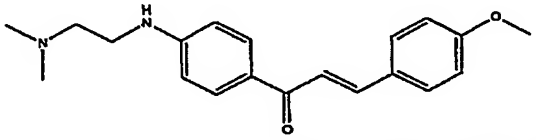


General procedure J gave the oxalate salt of title compound as yellow crystals in 48 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 98 (d, 2H), 7 86 (d, 1H), 7 80 (d, 1H), 7 73 (d, 1H), 7 71 (d, 1H), 7 50 (s, 1H), 6 88 (s, br, 1H), 6 68 (d, 2H), 3 90 (s, 3H), 3 85 (s, 3H), 3 50 (t, 2H), 3 20 (t, 2H), 2 80 (s, 6H)

I-056

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-phenyl)-propenone

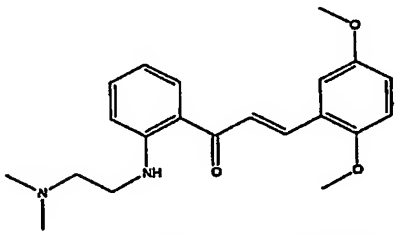


General procedure J gave the fumarate salt of title compound as yellow crystals in 45 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 98 (d, 2H), 7 86 (d, 1H), 7 82 (d, 2H), 7 73 (d, 1H), 7 00 (d, 2H), 6 88 (s, br, 1H), 6 68 (d, 2H), 6 55 (s, 2H), 3 82 (s, 3H), 3 26 (t, 2H), 2 70 (t, 2H), 2 40 (s, 6H)

I-057

(*E*)-3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

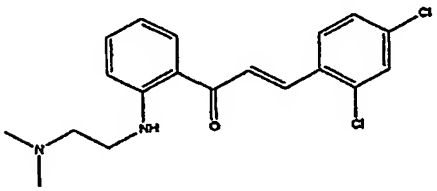


General procedure J gave the oxalate salt of title compound as orange crystals in 61 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 11 (t, 1H), 8 20 (d, 1H), 7 95 (s, 2H), 7 52 (d, 1H), 7 47 (t, 1H), 7 08-6 95 (m, 2H), 6 90 (d, 1H), 6 71 (t, 1H), 3 83 (s, 3H), 3 80 (s, 3H), 3 70-3 55 (m, 2H), 3 20 (t, 2H), 2 76 (s, 6H)

I-058

(*E*)-3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

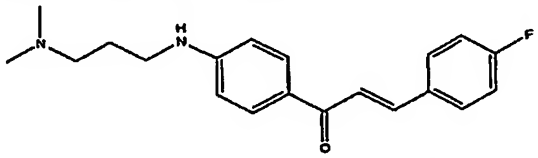


General procedure J gave the oxalate salt of title compound as yellow crystals in 69 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 13 (t, 1H), 8 24 (t, 2H), 8 08 (d, 1H), 7 90 (d, 1H), 7 72 (d, 1H), 7 56-7 40 (m, 2H), 6 93 (d, 1H), 6 70 (t, 1H), 3 70-3 58 (m, 2H), 3 20 (t, 2H), 2 75 (s, 6H)

I-059

(*E*)-1-[4-(3-Dimethylamino-propylamino)-phenyl]-3-(4-fluoro-phenyl)-propenone

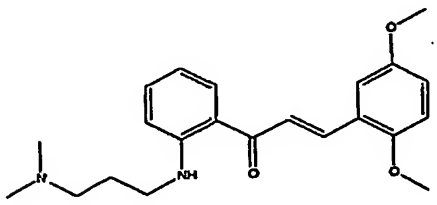


General procedure J gave the oxalate salt of title compound as yellow crystals in 64 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 99 (d, 2H), 7 93 (dd, 2H), 7 84 (d, 1H), 7 62 (d, 1H), 7 28 (t, 2H), 6 79 (s, br, 1H), 6 66 (d, 2H), 3 20 (t, 2H), 3 13-3 05 (m, 2H), 2 74 (s, 6H), 2 00-1 85 (m, 2H)

I-060

(*E*)-3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

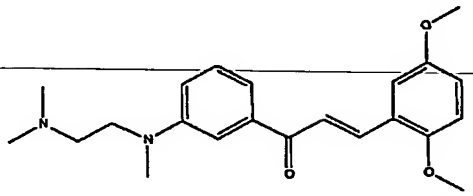


General procedure J gave the oxalate salt of title compound as orange crystals in 71 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 15 (t, br, 1H), 8 20 (d, 1H), 7 96 (s, 2H), 7 52 (d, 1H), 7 43 (t, 1H), 7 09-6 95 (m, 2H), 6 85 (d, 1H), 6 68 (t, 1H), 3 84 (s, 3H), 3 80 (s, 3H), 3 31 (t, 2H), 3 18-3 01 (m, 2H), 2 74 (s, 6H), 2 05-1 90 (m, 2H)

I-061

(*E*)-3-(2,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

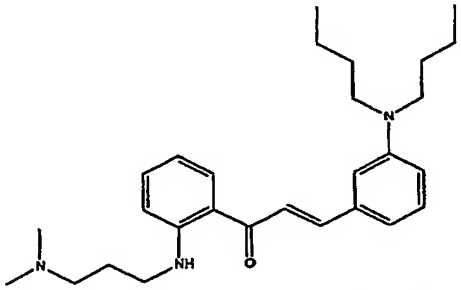


General procedure J gave the oxalate salt of title compound as yellow crystals in 44 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 98 (d, 1H), 7 82 (d, 1H), 7 50 (d, 1H), 7 43-7 30 (m, 2H), 7 27 (t, 1H), 7 08-7 02 (m, 2H), 6 97 (dd, 1H), 3 83 (s, 3H), 3 78 (s, 3H), 3 48 (t, 2H), 2 96 (s, 3H), 2 38 (t, 2H), 2 18 (s, 6H)

I-062

(*E*)-3-(3-Dibutylamino-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

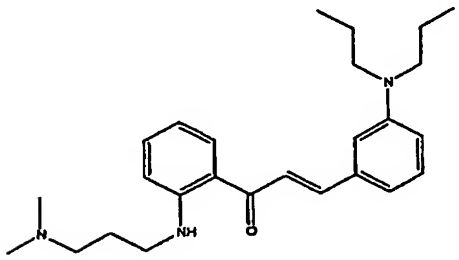


General procedure J gave the title compound as a orange oil in 40 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 14 (t, 1H), 8 11 (dd, 1H), 7 84 (d, 1H), 7 59 (d, 1H), 7 40 (t, 1H), 7 20 (t, 1H), 7 07 (d, 1H), 6 95 (s, 1H), 6 80 (d, 1H), 6 68 (dd, 1H), 6 62 (t, 1H), 3 35-3 20 (m, 6H), 2 32 (t, 2H), 2 15 (s, 6H), 1 80-1 68 (m, 2H), 1 57-1 43 (m, 4H), 1 41-1 25 (m, 4H), 0 92 (t, 6H)

I-063

(*E*)-1-[2-(3-Dimethylamino-propylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone

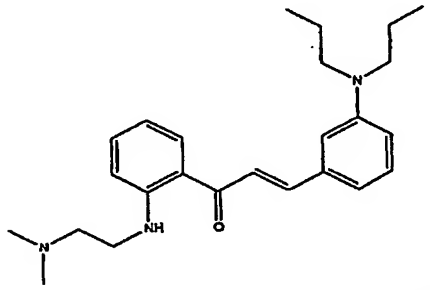


General procedure J gave the title compound as a red oil in 55 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 14 (t, 1H), 8 13 (dd, 1H), 7 85 (d, 1H), 7 60 (d, 1H), 7 40 (t, 1H), 7 20 (t, 1H), 7 08 (d, 1H), 6 97 (s, 1H), 6 80 (d, 1H), 6 68 (dd, 1H), 6 62 (t, 1H), 3 35-3 20 (m, 6H), 2 32 (t, 2H), 2 14 (s, 6H), 1 80-1 68 (m, 2H), 1 61-1 45 (m, 4H), 0 90 (t, 6H)

I-064

(*E*)-1-[2-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone

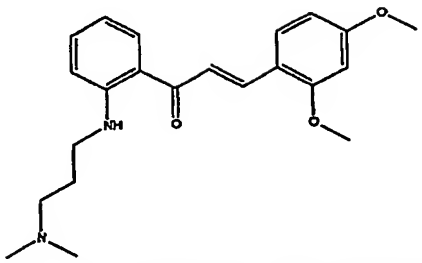


General procedure J gave the title compound as red oil in 54 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 20 (t, 1H), 8 13 (dd, 1H), 7 85 (d, 1H), 7 62 (d, 1H), 7 42 (t, 1H), 7 20 (t, 1H), 7 10 (d, 1H), 6 97 (s, 1H), 6 79 (d, 1H), 6 68 (dd, 1H), 6 63 (t, 1H), 3 35-3 20 (m, 6H), 2 52 (t, 2H), 2 20 (s, 6H), 1 62-1 45 (m, 4H), 0 90 (t, 6H)

I-065

(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

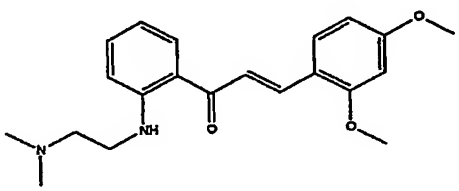


General procedure J gave the fumarate salt of title compound as yellow crystals in 43 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 12 (s, br, 1H), 8 11 (dd, 1H), 7 98-7 75 (m, 3H), 7 40 (td, 1H), 6 81 (d, 1H), 6 70-6 57 (m, 3H), 6 53 (s, 2H), 3 90 (s, 3H), 3 84 (s, 3H), 3 28 (t, 2H), 2 77 (t, 2H), 2 48 (s, 6H), 1 95-1 80 (m, 2H)

I-066

(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

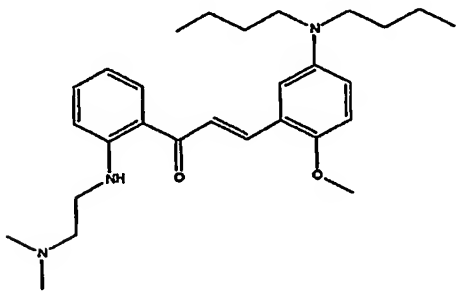


General procedure J gave the fumarate salt of title compound as yellow crystals in 58 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 13 (t, 1H), 8 10 (dd, 1H), 7 96-7 86 (m, 2H), 7 79 (d, 1H), 7 41 (td, 1H), 6 82 (d, 1H), 6 69-6 60 (m, 3H), 6 58 (s, 2H), 3 90 (s, 3H), 3 85 (s, 3H), 3 40-3 30 (m, 2H), 2 82 (t, 2H), 2 38 (s, 6H)

I-067

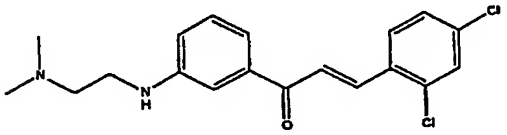
(*E*)-3-(5-Dibutylamino-2-methoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the title compound as a red oil in 63 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 15 (t, 1H), 8 04 (dd, 1H), 7 92 (d, 1H), 7 82 (d, 1H), 7 41 (t, 1H), 7 10 (d, 1H), 6 96 (d, 1H), 6 82-6 72 (m, 2H), 6 63 (t, 1H), 3 80 (s, 3H), 3 30-3 18 (m, 6H), 2 53 (t, 2H), 2 21 (s, 6H), 1 55-1 40 (m, 4H), 1 49-1 23 (m, 4H), 0 91 (t, 6H)

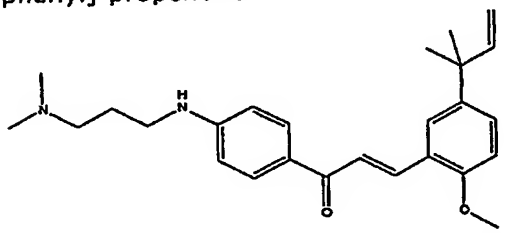
I-068
(*E*)-3-(2,4-Dichloro-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 56 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 21 (d, 1H), 7 91 (s, 2H), 7 75 (d, 1H), 7 54 (dd, 1H), 7 38 (d, 1H), 7 31-7 20 (m, 2H), 6 90 (d, 1H), 6 58 (s, 2H), 5 70 (t, 1H), 3 20-3 10 (m, 2H), 2 45 (t, 2H), 2 18 (s, 6H)

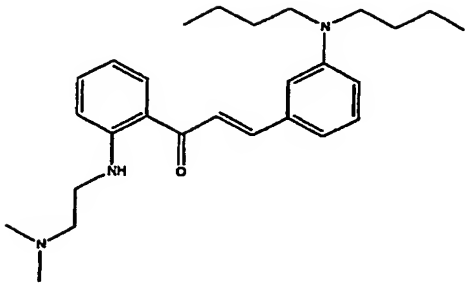
I-069
(*E*)-3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 45 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 00-7 82 (m, 3H), 7 79 (d, 2H), 7 33 (d, 1H), 7 01 (d, 1H), 6 75 (s, br, 1H), 6 65 (d, 2H), 6 57 (s, 2H), 6 08 (dd, 1H), 5 10-4 94 (m, 2H), 3 85 (s, 3H), 3 18 (t, 2H), 2 65 (t, 2H), 2 39 (s, 6H), 1 88-1 66 (m, 2H), 1 39 (s, 6H)

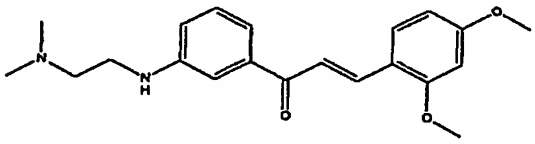
I-070
(*E*)-3-(3-Dibutylamino-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the title compound as an orange oil in 54 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 20 (t, 1H), 8 10 (dd, 1H), 7 83 (d, 1H), 7 61 (d, 1H), 7 40 (t, 1H), 7 19 (t, 1H), 7 08 (d, 1H), 6 95 (s, 1H), 6 78 (d, 1H), 6 70-6 56 (m, 2H), 3 35-3 18 (m, 6H), 2 50 (t, 2H), 2 20 (s, 6H), 1 58-1 41 (m, 4H), 1 40-1 25 (m, 4H), 0 92 (t, 6H)

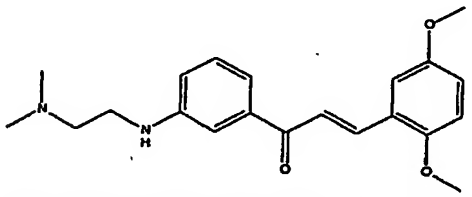
I-071.
(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 43 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 95 (d, 1H), 7 87 (d, 1H), 7 66 (d, 1H), 7 40-7 20 (m, 3H), 6 90 (d, 1H), 6 68-6 59 (m, 2H), 3 90 (s, 3H), 3 85 (s, 3H), 3 47 (t, 2H), 3 21 (t, 2H), 2 79 (s, 6H)

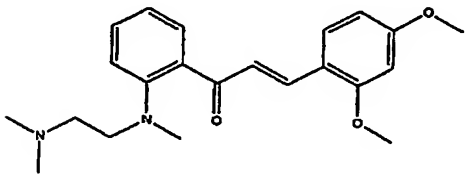
I-072
(*E*)-3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 27 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 73 (d, 1H), 7 55 (d, 1H), 7 26 (s, 1H), 7 18 (d, 1H), 7 07 (t, 1H), 7 01 (s, 1H), 6 80 (s, 2H), 6 68 (d, 1H), 3 58 (s, 3H), 3 52 (s, 3H), 3 20 (t, 2H), 2 95 (t, 2H), 2 79 (s, 6H)

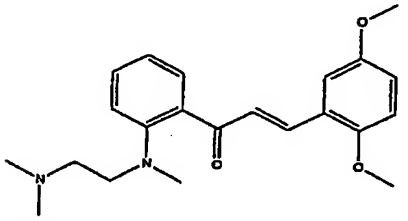
I-073
(*E*)-3-(2,4-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the title compound as yellow oil in 36 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 80 (d, 1H), 7 68 (d, 1H), 7 45-7 27 (m, 3H), 7 13 (d, 1H), 6 95 (t, 1H), 6 65-6 57 (m, 2H), 3 86 (s, 3H), 3 82 (s, 3H), 3 12 (t, 2H), 2 74 (s, 3H), 2 35 (t, 2H), 2 06 (s, 6H)

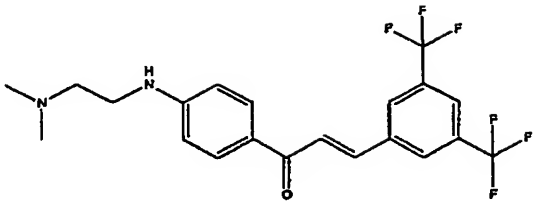
I-074
(*E*)-3-(2,5-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the title compound as a red oil in 83 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 83 (d, 1H), 7 48-7 36 (m, 3H), 7 27 (d, 1H), 7 15 (1H), 7 06-6 92 (m, 3H), 3 80 (s, 3H), 3 73 (s, 3H), 3 11 (t, 2H), 2 74 (s, 3H), 2 36 (t, 2H), 2 06 (s, 6H)

I-075
(*E*)-3-(3,5-Bis-trifluoromethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

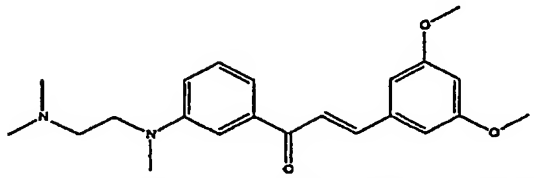


General procedure J gave the title compound as yellow solid in 36 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 10 (s, 2H), 7 95 (d, 2H), 7 88 (s, 1H), 7 77 (d, 1H), 7 67 (d, 1H), 6 66 (d, 2H), 5 08 (t, br, 1H), 3 30-3 18 (m, 2H), 2 59 (t, 2H), 2 27 (s, 6H)

I-076

(*E*)-3-(3,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

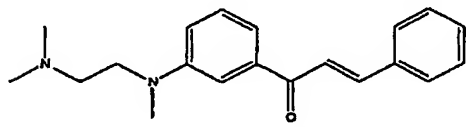


General procedure J gave the fumarate salt of title compound as yellow crystals in 32 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 88 (d, 1H), 7 65 (d, 1H), 7 49 (d, 1H), 7 40-7 26 (m, 2H), 7 10-6 92 (m, 3H), 6 58 (d, 2H), 3 80 (s, 6H), 3 61 (t, 2H), 2 62 (t, 2H), 2 39 (s, 6H)

I-077

(*E*)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-phenyl-propenone

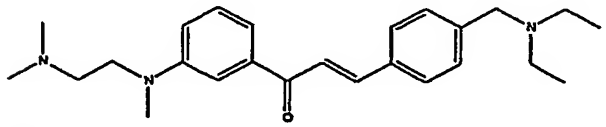


General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 92-7 83 (m, 3H), 7 72 (d, 1H), 7 50-7 43 (m, 4H), 7 40-7 30 (m, 2H), 7 08-7 02 (dd, 1H), 6 58 (s, 2H), 3 62 (t, 2H), 2 95 (s, 3H), 2 73 (t, 2H), 2 45 (s, 6H)

I-078

(*E*)-3-(4-Diethylaminomethyl-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

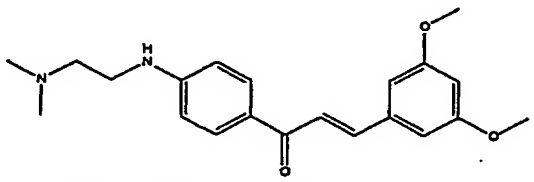


General procedure J gave the title compound as yellow oil in 25 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 93 (d, 1H), 7 72 (d, 2H), 7 63 (d, 1H), 7 58-7 41 (m, 5H), 7 40 (s, 2H), 7 10-7 04 (m, 1H), 3 72 (s, 2H), 3 65 (t, 2H), 3 16 (s, 3H), 2 73-2 60 (m, 6H), 2 45 (s, 6H), 1 19 (t, 6H)

I-079

(*E*)-3-(3,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

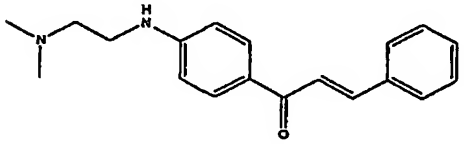


General procedure J gave the fumarate salt of title compound as yellow crystals in 50 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 00 (d, 2H), 7 88 (d, 1H), 7 54 (d, 1H), 7 00 (s, 2H), 6 68 (d, 3H), 6 55 (s, 2H), 3 80 (s, 6H), 3 35-3 20 (m, 2H), 2 65 (t, 2H), 2 35 (s, 3H)

I-080

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-phenyl-propenone

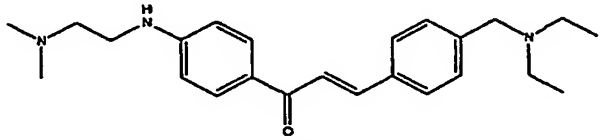


General procedure J gave the fumarate salt of title compound as yellow crystals in 45 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 98 (d, 2H), 7 94-7 80 (m, 3H), 7 62 (d, 1H), 7 50-7 38 (m, 3H), 6 75-6 65 (m, 3H), 6 57 (s, 2H), 3 31 (q, 2H), 2 67 (t, 2H), 2 36 (s, 6H)

I-081

(*E*)-3-(4-Diethylaminomethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

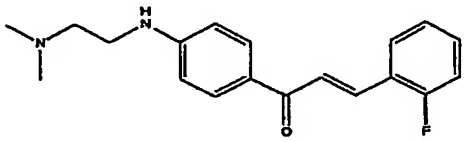


General procedure J gave the title compound as yellow oil in 36 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 98 (d, 2H), 7 90 (d, 1H), 7 63-7 52 (m, 3H), 7 39 (d, 2H), 6 64 (d, 2H), 4 95 (t, 1H), 3 60 (s, 2H), 3 23 (q, 2H), 2 60-2 48 (m, 6H), 2 29 (s, 6H), 1 06 (t, 6H)

I-082

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-fluoro-phenyl)-propenone

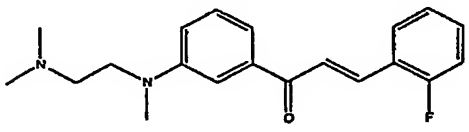


General procedure J gave the fumarate salt of title compound as yellow crystals in 50 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 08 (t, 1H), 8 02-7 88 (m, 3H), 7 74 (d, 1H), 7 54-7 43 (m, 1H), 7 37-7 25 (m, 2H), 6 76 (t, 1H), 6 68 (d, 2H), 6 57 (s, 2H), 3 32 (q, 2H), 2 66 (t, 2H), 2 35 (s, 6H)

I-083

(*E*)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-fluoro-phenyl)-propenone

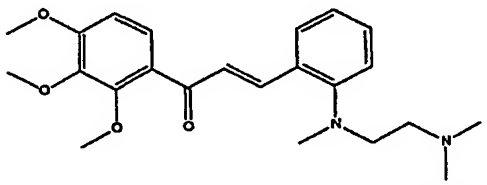


General procedure J gave the oxalate salt of title compound as yellow crystals in 26 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 12 (t, 1H), 7 94 (d, 1H), 7 82 (d, 1H), 7 58-7 47 (m, 2H), 7 45-7 28 (m, 4H), 7 13 (dd, 1H), 3 78 (t, 2H), 3 22 (t, 2H), 3 00 (s, 3H), 2 82 (s,

6H)

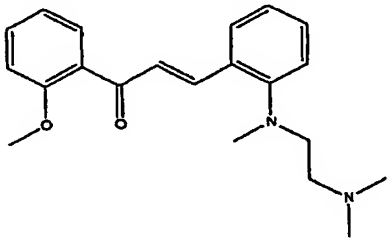
I-084
(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2,3,4-trimethoxy-phenyl)-propenone



General procedure J gave the title compound as yellow oil in 41 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 06 (d, 1H), 7 65 (dd, 1H), 7 48 (d, 1H), 7 43 (d, 1H), 7 34 (td, 1H), 7 11 (d, 1H), 7 04 (t, 1H), 6 77 (d, 1H), 3 97 (s, 3H), 3 95 (s, 3H), 3 94 (s, 3H), 3 10 (m, 2H), 2 80 (s, 3H), 2 52 (m, 2H), 2 22 (s, 6H)

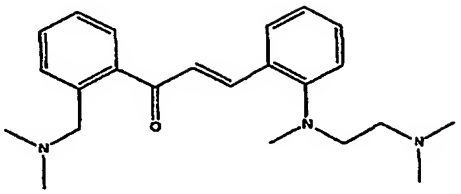
I-085.
(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-methoxy-phenyl)-propenone



General procedure J gave the title compound as yellow oil in 37 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 73 (d, 1H), 7 69 (dd, 1H), 7 53 (td, 1H), 7 46 (dd, 1H), 7 37 (td, 1H), 7 25 (d, 1H), 7 18 (d, 1H), 7 14 (d, 1H), 7 10-7 01 (m, 2H), 3 84 (s, 3H), 2 95 (t, 2H), 2 70 (s, 3H), 2 33 (t, 2H), 2 05 (s, 6H)

I-086
(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-
propenone

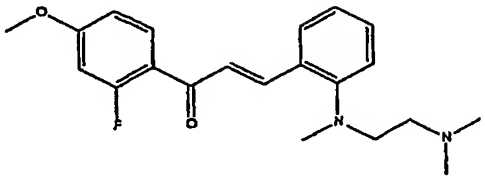


General procedure J gave the title compound as yellow oil in 58 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 67 (d, 1H), 7 62 (dd, 1H), 7 46-7 30 (m, 5H), 7 13-7 03 (m, 3H), 3 56 (s, 2H), 3 03 (t, 2H), 2 71 (s, 3H), 2 35 (t, 2H), 2 17 (s, 12H)

I-087

(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone

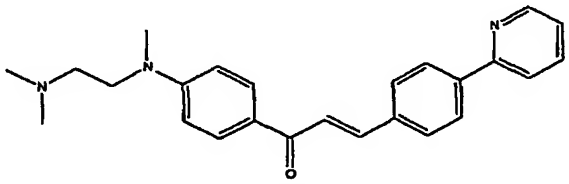


General procedure J gave the fumarate salt of title compound as yellow crystals in 41 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 92 (d, 1H), 7 83 (t, 1H), 7 76 (dd, 1H), 7 47-7 37 (m, 2H), 7 21 (d, 1H), 7 10 (t, 1H), 7 02-6 90 (m, 2H), 6 57 (s, 2H), 3 86 (s, 3H), 3 10 (t, 2H), 2 77-2 61 (m, 5H), 2 29 (s, 6H)

I-088:

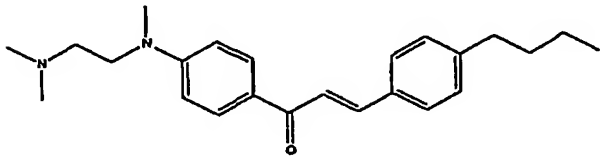
(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-pyridin-2-yl-phenyl)-propenone



General procedure J gave the title compound as a yellow solid in 35 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 73 (d, 1H), 8 09-8 02 (m, 4H), 7 87-7 75 (m, 5H), 7 66 (d, 1H), 7 31-7 24 (m, 1H), 6 74 (d, 2H), 3 57 (t, 2H), 3 10, (s, 3H), 2 54 (t, 2H), 2 30 (s, 6H)

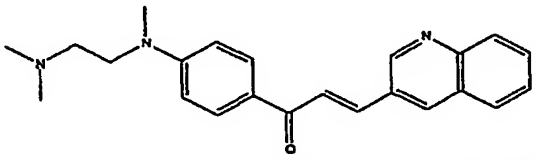
I-089
(*E*)-3-(4-Butyl-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 30 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 04 (d, 2H), 7 85 (d, 1H), 7 75 (d, 2H), 7 62 (d, 1H), 7 27 (d, 2H), 6 79 (d, 2H), 6 59 (s, 2H), 3 64 (t, 2H), 3 04, (s, 3H), 2 70-2 59 (m, 4H), 2 39 (s, 6H), 1 60-1 55 (m, 2H), 1 35-1 27 (m, 2H), 0 90 (t, 3H)

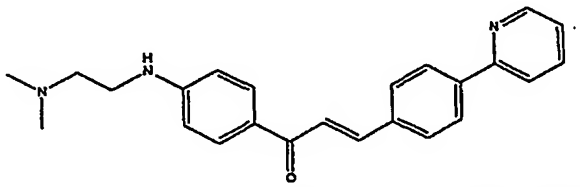
I-090
(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-3-yl-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 46 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 9 43 (d, 1H), 8 80 (d, 1H), 8 22 (d, 1H), 8 13-8 00 (m, 4H), 7,86-7 78 (m, 2H), 7 67 (dd, 1H), 6 83 (d, 2H), 6 60 (s, 3H), 3 67 (t, 2H), 3 06, (s, 3H), 2 71 (t, 2H), 2 42 (s, 6H)

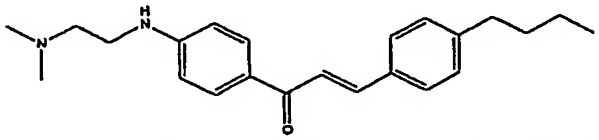
I-091
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-pyridin-2-yl-phenyl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 36 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 70 (d, 1H), 8 18 (d, 2H), 8 08-7 88 (m, 7H), 7,68 (d, 1H), 7 39 (ddd, 1H), 6 69 (d, 1H), 6 65 (t, 1H), 6 57 (s, 1H), 3 28, (q, 2H), 2 58 (t, 2H), 2 29 (s, 6H)

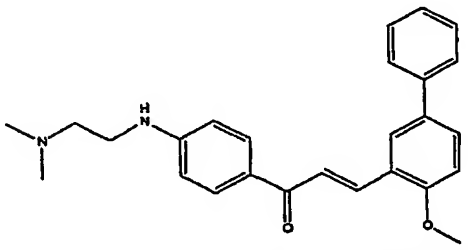
I-092.
(*E*)-3-(4-Butyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 35 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 83 (d, 2H), 7 69 (d, 1H), 7 61 (d, 2H), 7,46 (d, 1H), 7 13 (d, 2H), 6 54 (d, 2H), 6 48 (d, 1H), 6 43 (s, 1H), 3 12, (q, 2H), 2 51-2 42 (m, 4H), 2 16 (s, 6H), 1 46-1 41 (m, 2H), 1 22-1 14 (m, 2H), 0 77 (t, 3H)

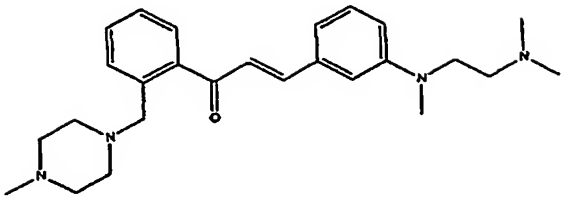
I-093
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 22 (d, 1H), 8 02-7 99 (m, 4H), 7 78-7 74 (m, 2H), 7,71 (d, 1H), 7 48 (dd, 2H), 7 36 (dd, 1H), 7 20 (d, 1H), 6 68 (d, 2H), 6 63 (t, 1H), 6 59 (s, 2H), 3 94 (s, 3H), 3 27, (q, 2H), 2 60 (t, 2H), 2 31 (s, 6H)

I-094
(*E*)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

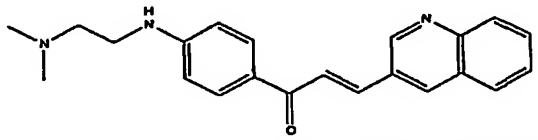


General procedure J gave the title compound as an orange oil in 33 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 44-7 32 (m, 4H), 7 24 (t, 1H), 7 18 (d, 1H), 7 00 (d, 1H), 6 88 (d, 1H), 6 82-6 73 (m, 2H), 3 60 (s, 2H), 3 48 (t, 2H), 2 98 (s, 3H), 2 49 (t, 2H), 2 48-2 34 (br, 8H), 2 30 (s, 6H), 2 20 (s, 3H)

I-095

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-3-yl-propenone

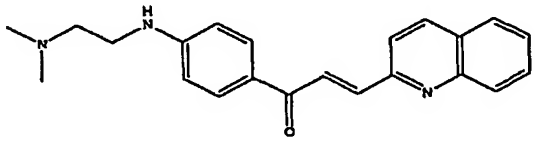


General procedure J gave the title compound as yellow solid in 37 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 9 23 (d, 1H), 8 34 (d, 1H), 8 14 (d, 1H), 8 03 (d, 2H), 7 95 (d, 1H), 7 89 (d, 1H), 7,81 (d, 1H), 7 79-7 74 (m, 1H), 7 61 (dd, 1H) 6 67 (d, 2H), 5 04 (t, 1H), 3 26, (dt, 2H), 2 61 (d, 2H), 2 29 (s, 6H)

I-096

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-2-yl-propenone

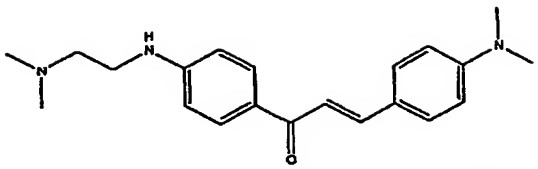


General procedure J gave the title compound as yellow solid in 17 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) 8 17-8 06 (m, 3H), 8 00 (d, 2H), 7 86 (d, 1H), 7 76 (d, 1H), 7 68 (dd, 1H), 7,59 (d, 1H), 7 49 (dd, 1H), 6 58 (d, 2H), 4 94 (t, 1H), 3 17, (dt, 2H), 2 52 (d, 2H), 2 20 (s, 6H)

I-097

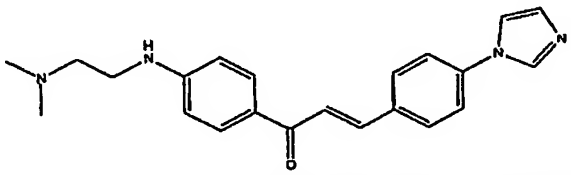
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-dimethylamino-phenyl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 20 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 06 (d, 2H), 7 78 (d, 2H), 7,70 (d, 2H), 6 86 (d, 2H), 6 78 (d, 2H), 6 70 (s, 2H), 6 65 (t, 1H), 3 39 (dt, 2H), 3 12 (s, 6H), 2 75 (t, 2H), 2 45 (s, 6H)

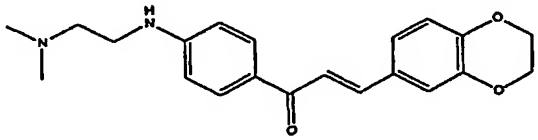
I-098
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-imidazol-1-yl-phenyl)-propenone



General procedure J gave the title compound as orange solid in 34 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 7 99 (d, 2H), 7,93 (t, 1H), 7 83-7 75 (m, 3H), 7 60 (d, 1H), 7 47 (d, 2H), 7 34 (t, 1H), 7 25 (t, 1H), 6 66 (d, 2H), 5 01 (t, 1H), 3 25, (dt, 2H), 2 60 (d, 2H), 2 29 (s, 6H)

I-099
(*E*)-3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

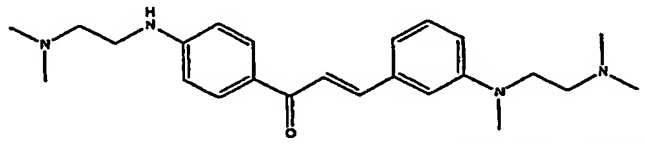


General procedure J gave the fumarate salt of title compound as yellow crystals in 13 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 97 (d, 2H), 7 74 (d, 1H), 7,52 (d, 1H), 7 43 (d, 1H), 7 31 (dd, 1H), 6 90 (d, 1H), 6 70-6 65 (m, 3H), 6 58 (s, 2H), 4 29 (bs, 4H), 3 34 (dt, 2H), 2 75 (t, 2H), 2 42 (s, 6H)

I-100

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

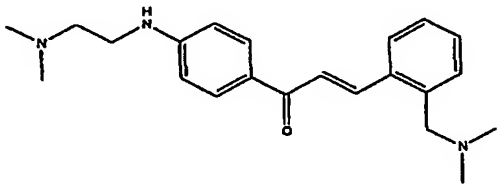


General procedure J gave the fumarate salt of title compound as yellow crystals in 15 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 97 (d, 2H), 7 80 (d, 1H), 7,57 (d, 1H), 7 23 (dd, 1H), 7 12-7 09 (m, 2H), 6 77 (dd, 1H), 6 68 (d, 2H), 6 62 (t, 1H), 6 57 (s, 2H), 3 54 (t, 1H), 3 28 (dt, 2H), 2 96 (s, 3H), 2 62-2-57 (m, 4H), 2 30 (s, 6H), 2 09 (s, 6H)

I-101

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

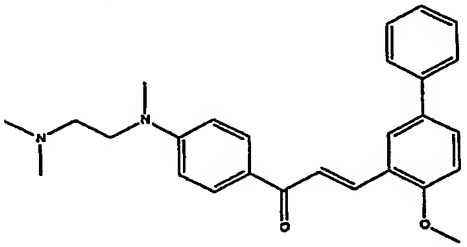


General procedure J gave the title compound as yellow solid in 10 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 24 (d, 1H), 8 00 (d, 2H), 7 76-7 73 (m, 1H), 7 70 (d, 1H), 7 37-7 32 (m, 3H), 6 65 (d, 1H), 4 95 (t, 1H), 3 57 (s, 2H), 3 25 (dt, 2H), 2 60 (t, 2H), 2 29 (s, 6H), 2 28 (s, 6H)

I-102

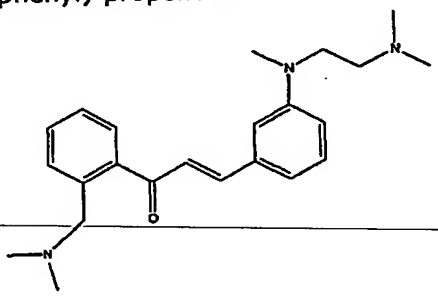
(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-biphenyl-3-yl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 36 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 23 (d, 1H), 8 07 (d, 2H), 8 02 (s, 2H), 7 78-7 71 (m, 3H), 7 48 (dd, 2H), 7,35 (d, 1H), 7 20 (d, 1H), 6 80 (d, 1H), 6 59 (s, 2H), 3 94 (s, 3H), 3 65 (t, 1H), 3 04, (s, 3H), 2 69 (t, 2H), 2 40 (s, 6H)

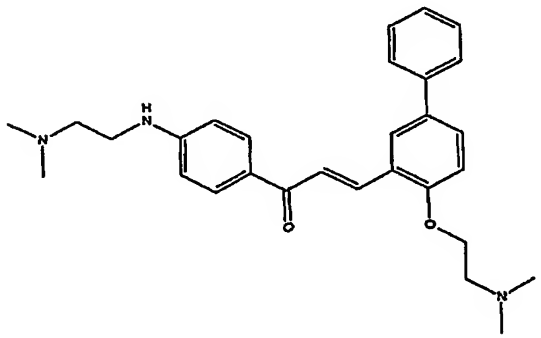
I-103
(*E*)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 42 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 54-7 38 (m, 4H), 7 27 (s, 2H), 7 22 (t, 1H), 7 05-6 98 (m, 2H), 6 81 (dd, 1H), 6 58 (s, 4H), 3 61 (s, 2H), 3 59 (t, 2H), 2 93 (s, 3H), 2 78 (t, 2H), 2 48 (s, 6H), 2 13 (s, 6H)

I-104
(*E*)-3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

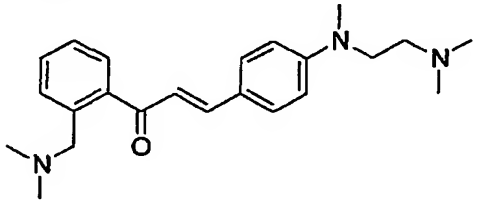


General procedure J gave the fumarate salt of title compound as yellow crystals in 14 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 8 16 (d, 1H), 8 08 (d, 1H), 8 01 (d, 2H), 7 96 (d, 1H), 7 75 (d, 2H), 7,70 (dd, 1H), 7 47 (dd, 2H), 7 35 (dd, 1H), 7 23 (d, 1H), 6 69 (d, 2H), 6 58 (s, 2H), 4 28 (t, 1H), 3 32 (dt, 2H), 2 89 (t, 2H), 2 70 (t, 2H), 2 38 (s, 6H)

I-105

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

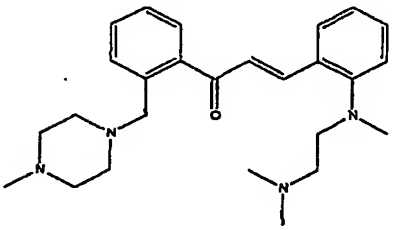


General procedure J gave the fumarate salt of title compound as orange crystals in 38 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 6-7 4 (m, 6H), 7 26 (d, 1H), 7 17 (d, 1H), 6 74 (d, 2H), 6 58 (s, 4H), 3 65 (s, 2H), 3 59 (t, 2H), 2 98 (s, 3H), 2 67 (t, 2H), 2 40 (s, 6H), 2 19 (s, 6H)

I-106

(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

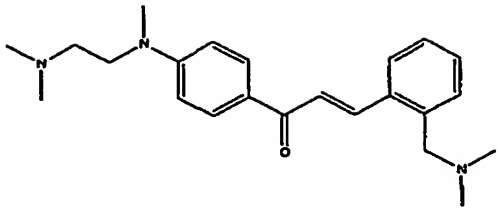


General procedure J gave the fumarate salt of title compound as yellow crystals in 59 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 78 (dd, 1H), 7 54 (d, 1H), 7 50-7 33 (m, 5H), 7 18 (d, 1H), 7 14-7 05 (m, 2H), 6 57 (s, 4H), 3 55 (s, 2H), 3 04 (t, 2H), 2 63 (s, 3H), 2 54 (t, 2H), 2 42-2 25 (br, 8H), 2 24 (s, 6H), 2 18 (s, 3H)

I-107

(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-dimethylaminomethyl-phenyl)-propenone

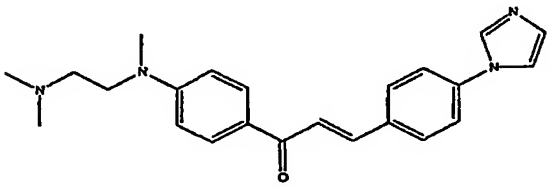


General procedure J gave the title compound as yellow oil in 33% yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 23 (d, 1H), 8 01 (d, 2H), 7 74-7 71 (m, 1H), 7 50 (d, 1H), 7 35-7 29 (m, 3H), 6 70 (d, 1H), 3 57-3 52 (m, 4H), 3 07 (s, 3H), 2 51 (t, 2H), 2 30 (s, 6H), 2 26 (s, 6H)

I-108

(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-imidazol-1-yl-phenyl)-propenone

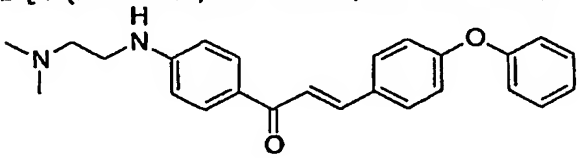


General procedure J gave the title compound as pale brown solid in 23 % yield

^{1}H-NMR(300 MHz, $CDCl_3$) δ 8 00 (d, 2H), 7 90 (t, 1H), 7 77 (d, 1H), 7 73 (d, 2H), 7 59 (d, 1H), 7 42 (d, 2H), 7 31 (t, 1H), 7 22 (t, 1H), 6 71 (d, 2H), 3 54 (t, 2H), 3 07, (s, 3H), 2 47 (t, 2H), 2 29 (s, 6H)

I-109

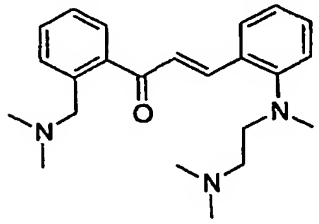
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-phenoxy-phenyl)-propenone



General procedure J gave the title compound as yellow crystals in 39 % yield

^{1}H NMR ($CDCl_3$) δ 7 98 (d, 2H), 7 78 (d, 1H), 7 63 (d, 2H), 7 51 (d, 1H), 7 42 (dd, 2), 7 18 (dd, 1H), 7 10-7 01 (m, 4H), 4 96 (t, 1H), 3 24 (dt, 2H) 2 60 (t, 2H), 2 29 (s, 6H)

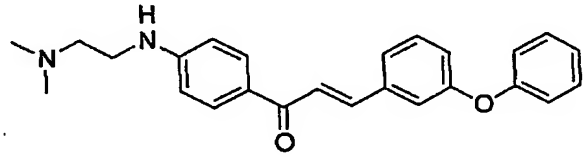
I-110
3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



General procedure J gave the title compound as a green oil in 58 % yield

^{1}H NMR (CDCl3) δ 7 66 (d, 1H), 7 60 (dd, 1H), 7 43 (m, 3H), 7 35 (m, 2H), 7 11 (d, 1H), 7 06 (d, 1H), 7 03 (d, 1H), 3 56 (s, 2H), 3 05 (t, 2H), 2 71 (s, 3H), 2 36 (t, 2H), 2 17 (s, 12H)

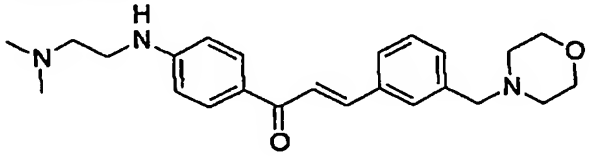
I-111
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-phenoxy-phenyl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 29 % yield

^{1}H NMR (DMSO) δ 7 78 (d, 2H), 7 70 (d, 1H), 7 43-7 37 (m, 3H), 7 27-7 17 (m, H), 6 95 (dt, 1H), 6 86-6 80 (m, 3H), 6 49-6 42 (m, 3H), 6 37 (s, 1H), 3 07 (q, 2H), 2 38 (t, 2H), 2 09 (s, 6H)

I-112
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone

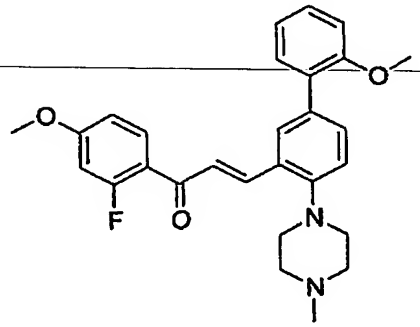


General procedure J gave the fumarate salt of title compound as yellow crystals in 37 % yield

^{1}H NMR (DMSO) δ 7 99 (d, 2H), 7 88 (d, 1H), 7 75-7 72 (m, 2H), 7 61 (d, 1H), 7 43-7 36 (m, 2H), 6 74-6 71 (m, 3H), 6 57 (s, 1H), 3 58 (t, 2H), 3 51 (s, 2H), 3 31 (q, 2H), 2 67 (t, 2H), 2 39-2 36 (m, 10H)

I-113

1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone

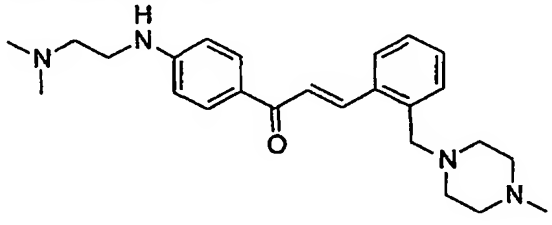


General procedure K gave the fumarate salt of title compound as yellow crystals in 33 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 76 (dd, 1H), 7 65 (t, 1H), 7 67 (d, 1H), 7 37 (dd, 1H), 7 29(dd, 1H), 7 20-7 15 (m, 2H), 7 02-6 75 (m, 5H), 6 44 (s, 3H), 3 70 (s, 3H), 3 61 (s, 3H), 2 81 (t, 4H), 2 45 (bs, 4H), 2 17 (s, 3H)

I-114

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

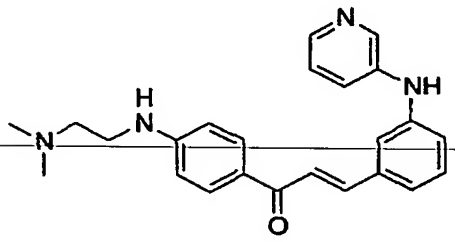


General procedure J gave the fumarate salt of title compound as yellow crystals in 11 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 93 (d, 1H), 7 85-7 81 (m, 3H), 7 58 (d, 1H), 7 25-7 21 (m, 3H, 6 63 (bs, 1H), 6 55 (d, 2H), 6 45 (s, 5H), 3 47 (s, 2H), 3 22 (q, 2H), 2 66 (t, 2H), 2 45 (bs, 2H), 2 32 (s, 6H), 2 20 (s, 3H)

I-115.

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

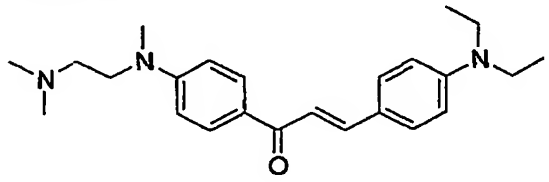


General procedure J gave the fumarate salt of title compound as brown-orange crystals in 6 % yield

^{1}H NMR (DMSO) δ 8 61 (bs, 1H), 8 53 (d, 1H), 8 21 (dd, 1H), 8 10 (dd, 2), 7 95 (d, 1H), 7 72 (d, 1H), 7 66 (dd, 1H), 7 61 (t, 1H), 7 56 (dt, 1H), 7 49 (t, 1H), 7 41 (dd, 1H), 7 30 (dd, 1H), 6 82 (d, 2H), 6 76-6 73 (m, 2H), 3 41, (q, 2H), 2 70 (t, 2H), 2 42 (s, 6H)

I-116

3-(4-Diethylamino-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

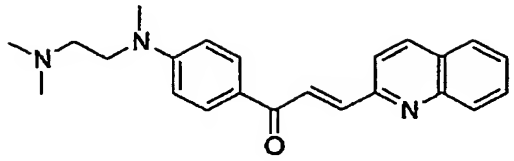


General procedure J gave the oxalate salt of title compound as yellow crystals in 4 % yield

^{1}H NMR (DMSO) δ 8 02 (d, 1H), 7 65-7 57 (m, 4H), 6 84 (d, 2H), 6 69 (d, 2H), 3 79 (t, 2H), 4 41 (q, 4H), 3 13 (t, 2H), 3 04 (s, 3H), 2 76 (s, 6H), 1 12 (t, 6H)

I-117

1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-2-yl-propenone

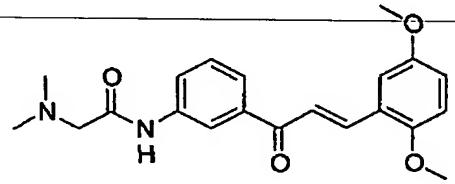


General procedure J gave the title compound as a brown oil in 18% yield

^{1}H NMR ($CDCl_3$) δ 8 24-8 08 (m, 5H), 7 93 (d, 1H), 7 82 (d, 1H), 7 75 (t, 1H), 7 66 (d, 1H), 7 55 (t, 1H), 7 73 (d, 1H), 3 58 (t, 2H), 3 09 (s, 3H), 2 56 (t, 2H), 2 33 (s, 6H)

I-118.

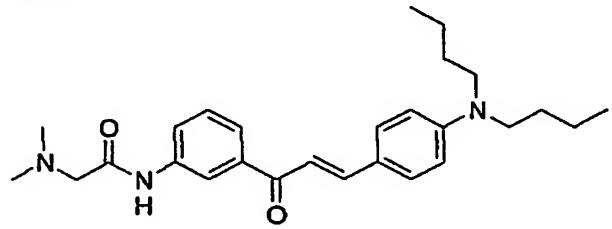
N-{3-[3,-(2,5-Dimethoxy-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide



General procedure J gave the fumarate salt of title compound as yellow crystals in 81 % yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 10 2 (s, 1H), 8 5 (t, 1H), 8 1 (m, 2H), 8 0 (m, 2H), 7 7 (t/s, 2H), 7 2 (bs, 2H), 6 8 (s, 2H), 4 0 (s, 3H), 3 9 (s, 3H), 3 3 (s, 2H), 2 7 (s, 6H)

I-119

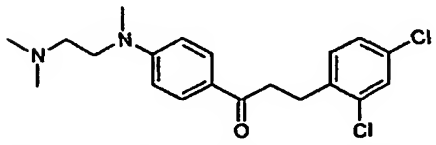


General procedure J gave the title compound as yellow oil in 32 % yield

^{1}H-NMR(300 MHz, CDCl3) δ 9 33 (bs, 1H), 8 04 (dd, 1H), 8 00 (t, 1H), 7 81 (d, 1H), 7 74 (dt, 1H), 7 53 (d, 2H), 7 46 (t, 1H), 7 31 (d, 1H), 6 63 (d, 2H), 3 34 (t, 4H), 3 13 (s, 2H), 2 42 (s, 6 H), 1 63 (m, 4H), 1 38 (six , 4H), 0 98 (t, 6H)

I-120

3-(2,4-Dichlorophenyl)-1-{4-[(2-dimethylamino-ethyl)methylamino]phenyl}-propan-1-one



General procedure M gave the fumaric salt of the title compound as yellow crystals in 7% yield

^{1}H-NMR(300 MHz, DMSO-d_6) δ 7 82 (d, 2H), 7 57 (d, 1H), 7 43 (d, 1H), 7 35 (dd, 1H), 6 73 (d, 2H), 6 58 (s, 2H), 3 58 (t, 2H), 3 19 (t, 2H), 3 00 (s, 3H), 2 98 (t, 2H), 2 59 (t, 2H), 2 33 (s, 6H)

Determination of metabolic stability

Incubations were performed with Wistar rat liver microsomes (0 5 mg/ml) in 2% sodium bicarbonate solution NADP (0 15 mg/ml), glucose-6-phosphate (0 5 mg/ml) and glucose-6-phosophate dehydrogenase (0 38 units/ml) were used as NADPH generation system and UDPGA (0 48 mg/ml) was added to include the phase II reaction, glucuronic acid conjugation, in the assay After 5 minutes of pre-incubation the reaction was started by addition of the test article to give a final concentration of 10µM Samples were incubated for 30 min at 37°C and the reactions were terminated by addition of equal volumes of acetonitrile Blank incubations were performed at the same concentration but without addition of microsomes

The fraction of compound metabolised during the 30 min incubation was determined quantitatively by HPLC with UV detection using a Waters Alliance 2690 separation module and the Waters 996 PDA-detector, Waters corp Milford, USA Samples were analysed on a XTerra RP_8 column (5µm) 4 6 x 150 mm (Waters corp , Milford, USA) with a linear gradient elution system Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile phase B (10mM ammonium acetate pH 9 5) During the first 20 minutes runtime, the mobile phase was changed to 90% A and 10% B followed by a fast 5 minutes gradient to return to initial conditions and a 5 minutes equilibration time The flow rate was 1 ml/min and injection volume 50µl

Determination of solubility

Solubility of the compounds was determined in 1M phosphate buffer pH 7 4 by preparation of suspensions in brown glass tubes The suspensions were rotated slowly for 24 hours Aliquots were centrifuged for 10 minutes at 10 000 rpm, supernatants were diluted in 50% acetonitrile prior to HPLC analysis and the concentrations in the samples were quantified against a standard curve The concentration of the compound in the supernatant is used as

term of solubility The HPLC method used for the assessment of solubility is the same as used in the in vitro metabolism assay

Biological testing

General methods

***In vitro* microbiological testing**

MIC determination in broth microdilution assay

Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus ATCC29213, Staphylococcus aureus ATCC33591, Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area), Enterococcus faecalis ATCC29212, Enterococcus faecium #17501 (vancomycin-resistant clinical isolate), Streptococcus pneumoniae #998 (clinical isolate), Streptococcus pyogenes #14813 (clinical isolate), Streptococcus agalactiae #19855 (clinical isolate), Escherichia coli ATCC25922 and Escherichia coli ESS*) The screening assay was done in 200 µl MH-broth cultures in microtitre plates For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by *NCLLS* (National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard – Fifth Edition M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria MICs for ATCC type strains fell within the limits posted by the *NCCLS* (National Committee for Clinical Laboratory Standards Performance Stadards for Antimicrobial Susceptibility Testing, Eleventh Informational Supplement M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin

MIC and MBC determination in broth macrodilution assay

MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5x10E5 CFU/ml as described by Amsterdam (Amsterdam, D Susceptibility testing of antimicrobials in liquid media *In* V Lorian (ed) Antibiotics in Laboratory Medicin 4 edition Williams & Wilkins 1996) MIC was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria Samples from cultures inhibited by test compound were plated onto unselective blood agar plates MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0 1% compared to the original inoculum

Killing Curve determination

For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5x10E5 CFU/ml as described for the MIC macrodilution assay above At the timepoints indicated 100 µl samples was withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar plates to determine CFU Test compounds with bactericidal activity is capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound An example of a bactericidal compound (I-031), which is primarily dependent on the concentration of the test compound is shown in Figure 4 An example of a bactericidal compound (I-070) which is primarily dependent on the incubation time with the compound is shown in Figure 5

MIC determination against Helicobacter pylori

Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the standards of NCCLS (National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard - Fifth Edition M7-A5 NCCLS 2000) MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 µl spots of a 2 McF suspension of the different strains of *H pylori* This inoculum corresponds to approximately 10E6 CFU/spot Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds

Activity determination against anaerobic bacteria

Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis,* an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria, Approved Standard - Fifth Edition M11-A5 NCCLS 2000) with the exception that Mueller-Hinton agar was used in place of supplemented Brucella broth Plates containing test compound at a single concentration (either 100 or 150 µM) were prepared in duplicate along with appropriate control plates Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not containg test compound

Leishmania promastigote assay

A WHO reference vaccine strain of *L major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks Salts containing 0 02 mg/ml gentamycin, 25 mM HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS) Incubation was carried out at 27°C Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth

The effect of test compounds on promastigotes was assessed by a method modified from Pearson et al Briefly, promastigotes (0 8x10^6/well) were incubated in 200 µl duplicate cultures either with a dilution series of test compound or medium alone in 96 wells flat bottom microtiter plates After 2h of incubation, 1 5 µCi of 3H-thymidine was added to each well and further incubated for 18 hours The cultures were then harvested on Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and counted in a TopCount-NXT microplate scintillation counter (Packard Instruments)

Plasmodium falciparum assay

Plasmodium falciparum 3D7 was maintained in culture by a modification of the method originally described by Trager and Jensen In brief, the parasites were grown in suspensions of human blood group 0 erythrocytes (RBC) maintained in RPMI1640 medium supplemented with 4 5 g/l Albumax II (Invitrogen), 10 mM hypoxantine, 1 4 mM L-glutamine and 0 05 mg/ml gentamicin Cultures were incubated at 37°C in atmosphere of 92 5% nitrogen, 5 5% carbon dioxide, and 2% oxygen To obtain synchronized cultures og parasites erythrocytes infected with late trophozoite and schizont stages were separated from ring stages and uninfected RBC by magnet-activated cell sorting (MACS, Miltenyi BioTec) (Staalsoe, T , H A Giha, D Dodoo, T G Theander, and L Hviid 1999 Detection of antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow cytometry Cytometry 35 329-336) Because of their high content of paramagnetic haemozoin, erythrocytes infected with late developmental stages of malaria parasites are specifically retained within the column The column was washed with PBS supplemented with 2% foetal calf serum and then the column was removed from the magnet and the retained late developmental stages of parasites were eluted and cultured for an additional 18 hours At this time the culture is highly synchronous containing more than 90% ring stages

These synchronized cultures of ring stage parasites were used to assay for antimalarial parasites Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by addition of uninfected RBC Then, these were incubated in 125 µl duplicate cultures containing 2 5x10^7 RBC/well with either a dilution series of test compound or with medium alone Plates were then incubated at 37°C for 24 hours when cultures were labelled by the addition 1 1 µCi 3H-phenyalanine and incubated overnight Then, the cultures were harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed extensively with water followed by a wash with 10% H_2O_2 to bleach hemoglobin Filter plates were counted in a TopCount-NXT microplate scintillation counter (Packard Instruments)

DHODH Assay

100 µl chalcone or 0 1 M Tris-HCl pH 8 0 is added to a well in a 96-wells microtiter plate Then 50 µl enzyme dilution is added The microtiter plate is placed in the Powerwave$_x$340 and the enzymatic reactions starts when adding 100 µl assay mixture The reaction are

measured every 20 sec for 10 min The samples with chalcones are compared with the samples with 0 1 M Tris-HCl pH 8 0 and the percent inhibition is calculated

Enzyme dilution The solution of recombinant purified enzyme is dissolved in 0 1 M Tris-HCl pH 8 to give an initial velocity of 0 04 - 0 05 ΔA/min

2,6-dichlorophenolindophenol (DCIP)-stock solution 40 mg DCIP and 10 ml 99 % Ethanol are mixed for 10 min at RT Then 100 µl 1 0 M Tris-HCl pH 8 and miliQ H_2O are added to a final volume of 100 ml The A_{600} of the DCIP-stock solution are measured in a microtiter plate on the Powerwave$_x$340 (Bio-Tek Instruments,Inc)

Dihydroorotate dehydrogenase (DHODH)-stock solution 25 mM dihydroorotate stock-solution is prepared by first dissolving in the same amount of mol NaOH and then miliQ H_2O is added to the final volume

Assay mix (10 ml solution) 600 µl of DHODH-stock solution and X ml (depending on the A_{600} value of stock-solution) DCIP to a final A_{600} = 2 5 are mixed Then 0 1 M Tris-HCl pH 8 0 are added to a final volume of 10 ml

Preparation of compound soluton A 10 mM stock-solution of compound (e g a chalcone derivative) is made in dimethylsulfoxid (DMSO) The compound is then diluted in 0 1 M Tris-HCl pH 8 to the test concentrations The final DMSO concentration in the sample is 10%

Biological Results

Licochalcone A (LicA) and 4'methoxy chalcone (4'MC) described in WO 93/17671 are used as reference compounds in the following discussion

Activity against non-fastidious bacteria

Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-positive non-fastidious bacteria including *Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Streptococcus agalactiae* Licochalcone A maintains its activity also against antibiotic resistant bacteria, e g *Staphylococcus aureus ATCC33591* (resistant to methicillin) and *Enterococcus faecium #17051* (resistant to vancomycin) In contrast, Licochalcone A have only modest or no activity against the prototype pathogenic Gram-negative bacterium, *Escherichia coli* 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial effect at all

In comparison with Licochalcone A, diaminochalcones retain the activity of Licochalcone A against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf Table SS) The diaminochalcones exhibit increased potency against Gram-positive pathogens (e g I-062, I-064, I-067, I-070, I-089, I-102) In contrast to Licochalcone A,

diaminochalcones exhibit activity against *Eschericia coli* Thus, several diaminochalcones (e g I-041, I-044, I-046, I-051, I-068, I-089, I-104, I-109, I-111, I-113) obtain MICs on 75 µM against *E coli ATCC25922* and on 9 4-18 8 µM against the general more susceptible ESS strain of *E coli* This indicates the potential use of diaminochalcones in the treatment of infections with Gram-negative bacteria

In the treatment of severe infections in immunocompromised patients bactericidal action of a antibiotic is a necessity As exemplified in Figures 4 and 5, diaminochalcones retain the bactericidal action of Licochalcone A For some diaminochalcones the bactericidal action is predominantly dependent on the concentration of the compound (e g I-031, cf Figure 4), for others the bactericidal action is predominantly dependent on the time of incubation with the compound (e g I-070, cf Figure 5) This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials

Tabel SS Comparasion of the effect of diamino-chalcones and Licochalcone/4'MC on bacteria, MIC values in µM

	A	B	C	D	E	F	G	H
LICA	**37 5**	**37 5**	**37 5**	**37 5**	**37 5**	**75 0**		**300 0**
4'-MC	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
I-031	18 8	37 5	18 8	18 8	18 8	37 5	150 0	18 8
I-041	18 8	37 5	18 8	18 8	18 8	37 5	75 0	18 8
I-044	18 8	18 8	18 8	18 8	18 8	37 5	75 0	18 8
I-047	18 8	18 8	37 5	37 5	37 5	37 5	300 0	18 8
I-051	18 8	18 8	37 5	18 8	18 8	37 5	75 0	18 8
I-062	9 4	9 4	9 4	9 4	9 4	18 8		18 8
I-063	18 8	18 8	18 8	37 5	18 8	37 5		18 8
I-064	9 4	18 8	18 8	18 8	18 8	18 8		18 8
I-067	9 4	9 4	9 4	18 8	9 4	18 8		75 0
I-068	18 8	37 5	37 5	37 5	18 8	37 5	75 0	18 8
I-069	18 8	18 8	18 8	18 8	18 8	37 5	150 0	9 4
I-070	4 7	4 7	9 4	9 4	9 4	18 8		300 0
I-075	37 5	37 5	37 5	37 5	37 5	37 5		9 4
I-089	9 4	18 8	9 4	9 4	9 4	18 8	300 0	9 4
I-092	18 8	18 8	9 4	4 7	9 4	18 8	75 0	9 4
I-102	9 4	9 4	9 4	9 4	9 4	37 5		9 4
I-104	*37 5*	*37 5*	*37 5*	*75 0*	*75 0*	*37 5*	*75 0*	*18 8*
I-109	18 8	18 8	18 8	18 8	18 8	37 5	150 0	18 8
I-111	18 8	18 8	37 5	18 8	9 4	37 5	150 0	9 4
I-113	4 7	9 4	9 4	18 8	9 4	37 5		9 4

A *Staphylococcus aureus ATCC29213,* ***B*** *Staphylococcus aureus ATCC33591,* ***C*** *Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area),* ***D*** *Enterococcus faecalis ATCC29212,* ***E*** *Enterococcus faecium #17501 (vancomycin-resistant clinical isolate),* ***F*** *Streptococcus pneumoniae #998 (clinical isolate),* ***G*** *Eschericia coli ATCC25922 and* ***H*** *Eschericia coli ESS* NA no activity

Activity against Helicobacter pylori

Colonization of the gastric mucosa with *Helicobacter pylori* is an important pathogenic determinant for the development of gastritis and peptic ulcer Diaminochalcones exhibit activity against *Helicobacter pylori* Several diaminochalcones (e g I-048, I-058, I-068, I-077, I-089, I-090, I-096, I-102) exhibit MICs in the range between 25 μM and 100 μM when tested against a panel of six strains *Helicobacter pylori*, that includes strains resistant to metronidazole Metronidazol is an antibiotic commonly included in treatment regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer The activity of diaminochalcones against both metronidazole-resistant and sensitive *Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment of *Helicobacter* infections

Activity against anaerobic bacteria

Diaminochalcones have been assayed in a single concentration of compound (100 μM) for activity against a panel of anaerobic bacteria containing common human pathogenic bacteria (*Bacteroides fragilis, Clostridium perfringens, Clostridium difficele*) Several diaminochalcones (e g I-051, I-062, I-064, I-067, I-068, I-070, I-075, I-089 and I-102) exhibit activity against all microorganisms within the test panel This clearly indicates the potential use of diaminochalcones in treatment of infection caused by anaerobic bacteria

Activity against protozoa

Activity against Leishamania major

Leishamania major is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and causing cutaneous leishmaniasis or kala-azar in humans Licochalcone A exhibit activity against *Leishmania* parasites and has shown efficacy in experimental animal models of cutaneous and visceral *Leishmania* infection (Chen et al , 1994) Diaminochalcones exhibit activity *in vitro* against *Leishamania major* with significantly improved potency compared to Licochalcone A and 4'MC (cf Table WW) The results clearly indicate the potential use of diaminochalcones in the treatment of *Leishamania* infection

Table WW. Effect of diamino-chalcones on *L major*

Comp	IC_{50} in μM
LICA	5 0
4'MC	5 6
I-044	1 1
I-045	1 7
I-046	1 7

I-047	1 1
I-051	0 8
I-054	1 7
I-061	1 8
I-064	1 8
I-067	1 7
I-068	1 0
I-070	1 6
I-075	2 0
I-076	0 5
I-077	1 7
I-083	1 4
I-088	0 5
I-096	0 9
I-113	0 5

Activity against Plasmodium falciparum

Plasmodium falciparum is a protozoan parasite transmitted by the mosquito, *Anopheles*, and causing malignant or severe malaria in humans Licochalcone A exhibit activity against *Plasmodium falciparum in vitro* and protects mice from infection with *P yoelii* and *P berghei* (Chen et al , 1994) Diaminochalcones exhibit activity *in vitro* against *Plasmodium falciparum* and several diaminochalcones exhibit improved potency compared to Licochalcone A (cf Table TT and Figure 6) The results clearly indicate the potential use of diaminochalcones in the treatment of malaria

Table TT Activity against *Plasmodium falciparum 3D7*

Comp	IC_{50} in µM
LICA	5 9
4'MC	40 0
I-040	3 3
I-074	4 5
I-075	3 6
I-084	2 1
I-087	2 9
I-093	2 4
I-094	2 3
I-103	0 6
I-104	1 2
I-107	3 5
I-108	4 8

Metabolism

The usefulness of chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* (Lica 100% turn-over *in vitro* and $t_{½}$= 10 min *in vivo*)

The introduction of a diamino group in the chalcone changes the metabolic properties, this is clear from Table QQ where the metabolic turn-over of a number of diamino-chalcones are compared to LicA The diamino-chalcones prepared are expected to show low or no metabolism *in vivo* as the metabolic turn-over are between 0-20% (compared to 100% turn-over for Lica) Consequently the half-life of a diamino-chalcone will be longer, reducing the dose needed for treatment

Table QQ Metabolic turn-over in vitro (%)

LICA	**100 0**
I-030	9 5
I-036	0 0
I-037	13 4
I-040	0 0
I-042	0 0
I-049	10 0
I-052	17 3
I-054	0 0
I-057	0 0
I-061	0 0
I-063	1 6
I-064	0 0

Inhibition of DHODH

Several of the diamino-chalcones prepared are potent inhibitors of DHODH The compounds are as potent as LicA and by far more potent than ordinary chalcones exemplified by 4'MC

Table DD Inhibition of DHODH

Comp	Inhibition (%)
LICA	**24 5**
4'MC	**7 0**
I-031	17 5
I-041	18 5
I-044	25 0
I-046	22 5

I-047 21 5
I-051 20 5
I-058 21 0
I-063 16 5
I-087 16 5

Solubility

The solubility of the neutral chalcones descibed in WO 93/17671 was very low A representative chalcone 4'-methoxy-chalcone has a solubility <0 05 mg/ml A few chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the molecule LicA has a solubility of 0 2 mg/ml

The diamino-chalcones described in this application are by far superior having solubility numbers in mg/ml Representative examples are

I-036 2 mg/ml
I-052 9 0 mg/ml
I-074 1 2 mg/ml
I-085 3 2 mg/ml

The high solubility means that dissolution and hence absorption will be nc problem This will inevitably cause a dramatic reduction of the dose needed making the diamino-chalcones very usefull as drug candidates

Conclusion

The use of chalcones as drug candidates for the treatment of parasitic or bacterial infections have been limited by the low in vivo potency (50mg/kg for LicA) of the compounds and a narrow spectrum of activity

Several factors contribute to the low in vivo potency Fast metabolism resulting in short half-lives in vivo, Low/no solubility in the intestine and consequently low/no absorption, Medium potency of the compounds against parasites and no activity against bacteria (except for LicA)

The diamino-chalcones in this application are expected to fulfill the criteria for a drug candidate The metabolism is low, the solubility is high and the compounds are potent against parasites as well as (resistant) Gram positive and Gram negative bacteria

CLAIMS

1 A compound of the general formula

$$Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}V\text{-}Ar^2(X^2)Y^2$$

wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

V designates $-CH_2-CH_2-$, -CH=CH- or -C≡C-, preferably -CH=CH-,

one or both of Y^1 and Y^2 independently represent at least one, such as 1-2, e g one, diamino-functional substituent(s) of the formula

$$-NR^3\text{-}Z\text{-}N(R^1)R^2$$

wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each R^H is independently selected from hydrogen and C_{1-6}-alkyl, or two R^H on the same carbon atom may designate =O,

R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring,
R^3 is selected from hydrogen, C_{1-6}-alkyl, and C_{1-6}-alkylcarbonyl, said alkyl and alkylcarbonyl optionally carrying substituent(s) selected from halogen, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, and aryl optionally substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, or R^1 and R^3 together form a biradical Z^* which is as defined for Z,

X^1 and X^2 independently designates 0-5, preferably 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally

substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl-oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine,

and salts thereof

2 The compound according to claim 1, wherein R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl

3 The compound according to any of the preceding claims, wherein R^3 is selected from hydrogen and methyl, in particular methyl

4 The compound according to any of the preceding claims, wherein X^1 and X^2 independently designates 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, guanidino, carbamido, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, optionally substituted C_{1-6}-alkylthio, aminosulfonyl, mono- and di(C_{1-6}-

alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen

5 The compound according to any of the preceding claims, wherein R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6}-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl

6 The compound according to any of the preceding claims, wherein X^1 and X^2 independently designates 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen

7 The compound according to any of the preceding claims, wherein V designates -CH=CH-

8 The compound according to any of the preceding claims, wherein at least one of Ar^1 and Ar^2, preferably both, are aromatic rings, in particular phenyl rings

9 The compound according to claim 8, wherein both of Ar^1 and Ar^2 are phenyl rings and Y^1 represent at least one diamino-functional substituent

10 The compound according to any of the preceding claims, wherein X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen

11 The compound according to any of the preceding claims, wherein X^2 represents at least two halogen atoms

12 The compound according to any of the preceding claims, wherein at least one or Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl

13 The compound according to any of the preceding claims, wherein Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3

14 The compound according to any of the preceding claims, wherein one of Y^1 and Y^2 represent a substituent of the formula

$$-NR^3-(CH_2)_{2\ 3}-N(R^1)R^2$$

wherein R^3 is selected from hydrogen and methyl, R^1 and R^2 is selected from hydrogen and $C_{1\ 6}$-alkyl

15 A compound according to claim 14, wherein V is -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings

16 A pharmaceutical composition comprising a compound as defined in any of the claims 1-15 in combination with a pharmaceutically acceptable carrier

17 A compound as defined in any of claims 1-15 for use as a drug substance

18 The use of a compound as defined in any of the claims 1-15 for the preparation of a pharmaceutical composition for the treatment of bacterial infections in a mammal in need thereof

19 The use according to claim 18, wherein the bacterial infection is caused by a bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria, and anerobic bacteria

20 The use according to claim 19, wherein the bacteria is a microaerophilic bacteria, e g a bacteria associated with gastric disease, such as *Helicobacter pylori*

21 The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S aureus*

22 The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E faecium*

23 The use according to claim 19, wherein the bacteria is selected from a *S pneumoniae* and *S pyogenes*

24 The use according to claim 19, wherein the bacteria is a member of *Enterobacteriaceae*, e g E coli

25 The use according to claim 19, wherein the bacteria is a pathogenic anaerobic bacteria, e g *Bacteroides fragilis* or *Clostridium species*

26 The use of a compound as defined in any of claims 1-15, for the preparation of a pharmaceutical composition for the treatment of infections caused by protozoa in a mammal

27 The use according to claim 26, wherein the infection is caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*

28 The use of a compound as defined in any of the claims 1-15, for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp*

29 The use according to claim 28, wherein the infection is cutaneous and/or visceral

30 A method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B

31 The method according to claim 30, wherein the chemical compound is a chalcone derivative

32 The method according to claim 30, wherein the chemical compound is a chalcone derivative as defined in any of the claims 1-15

Figure 1

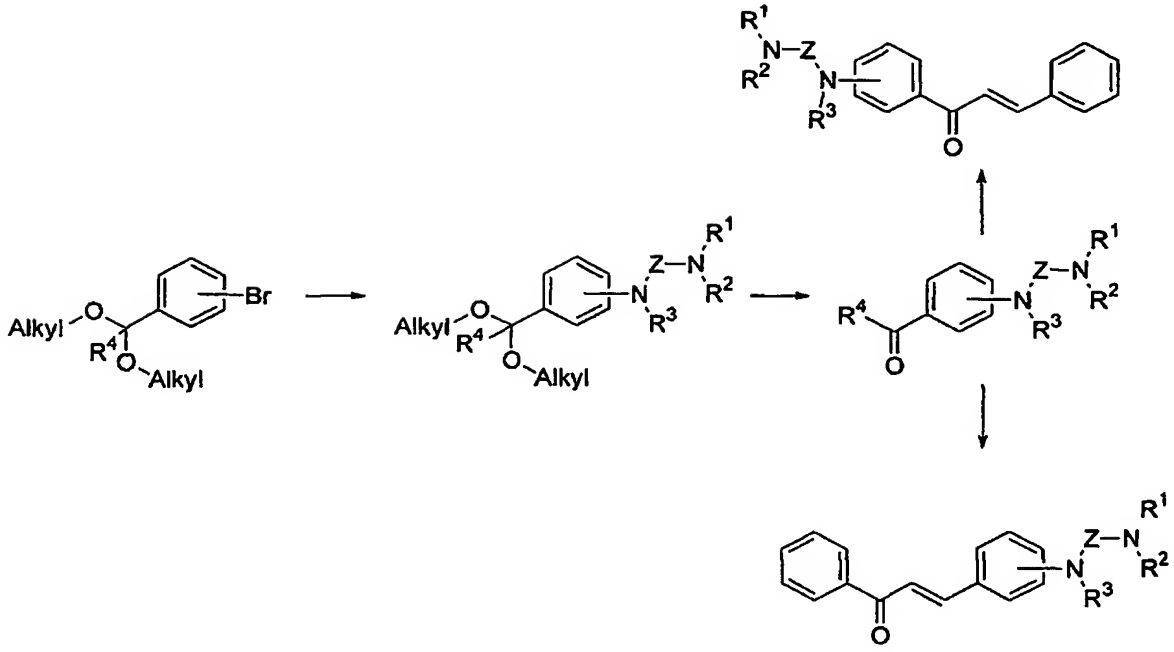


Figure 2

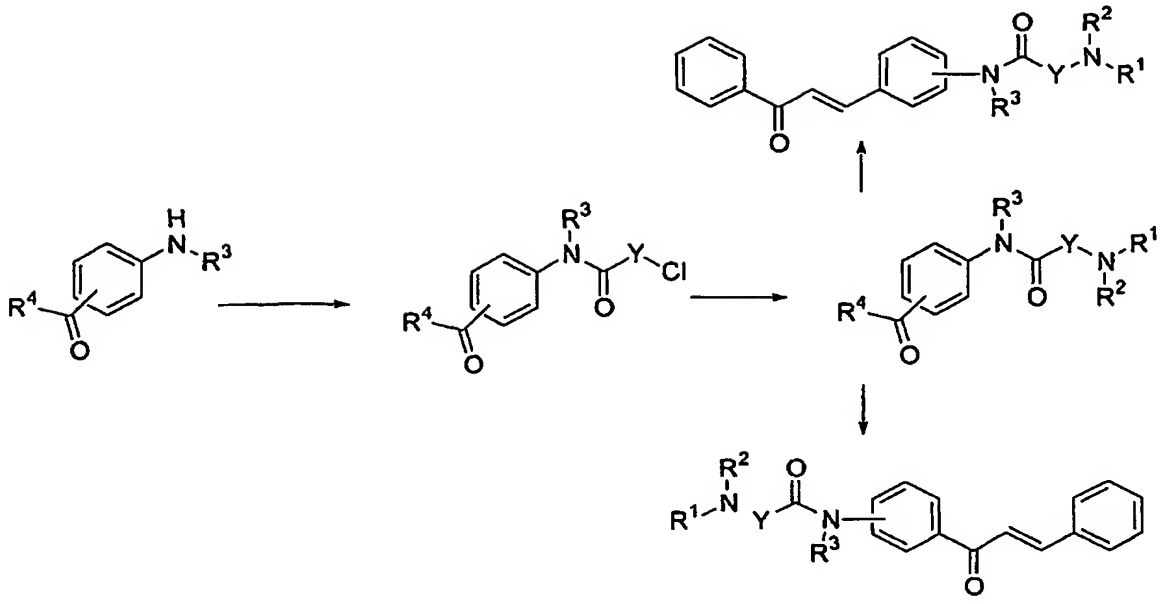
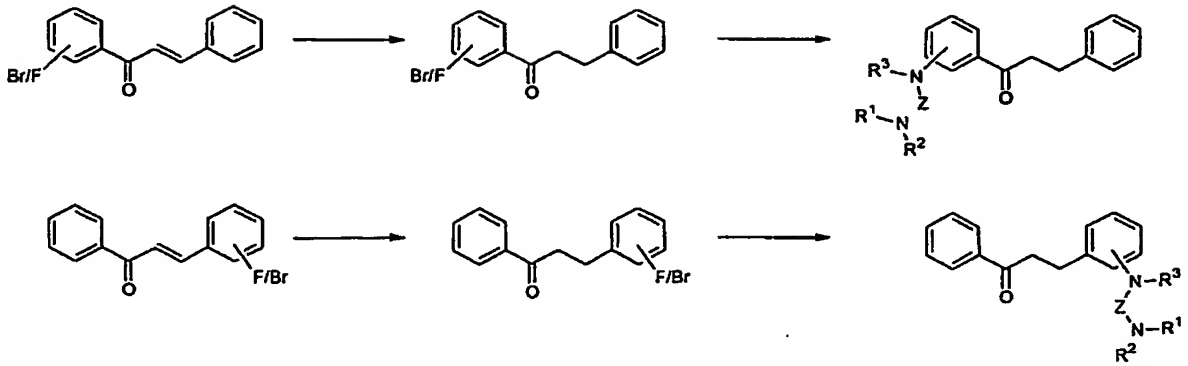
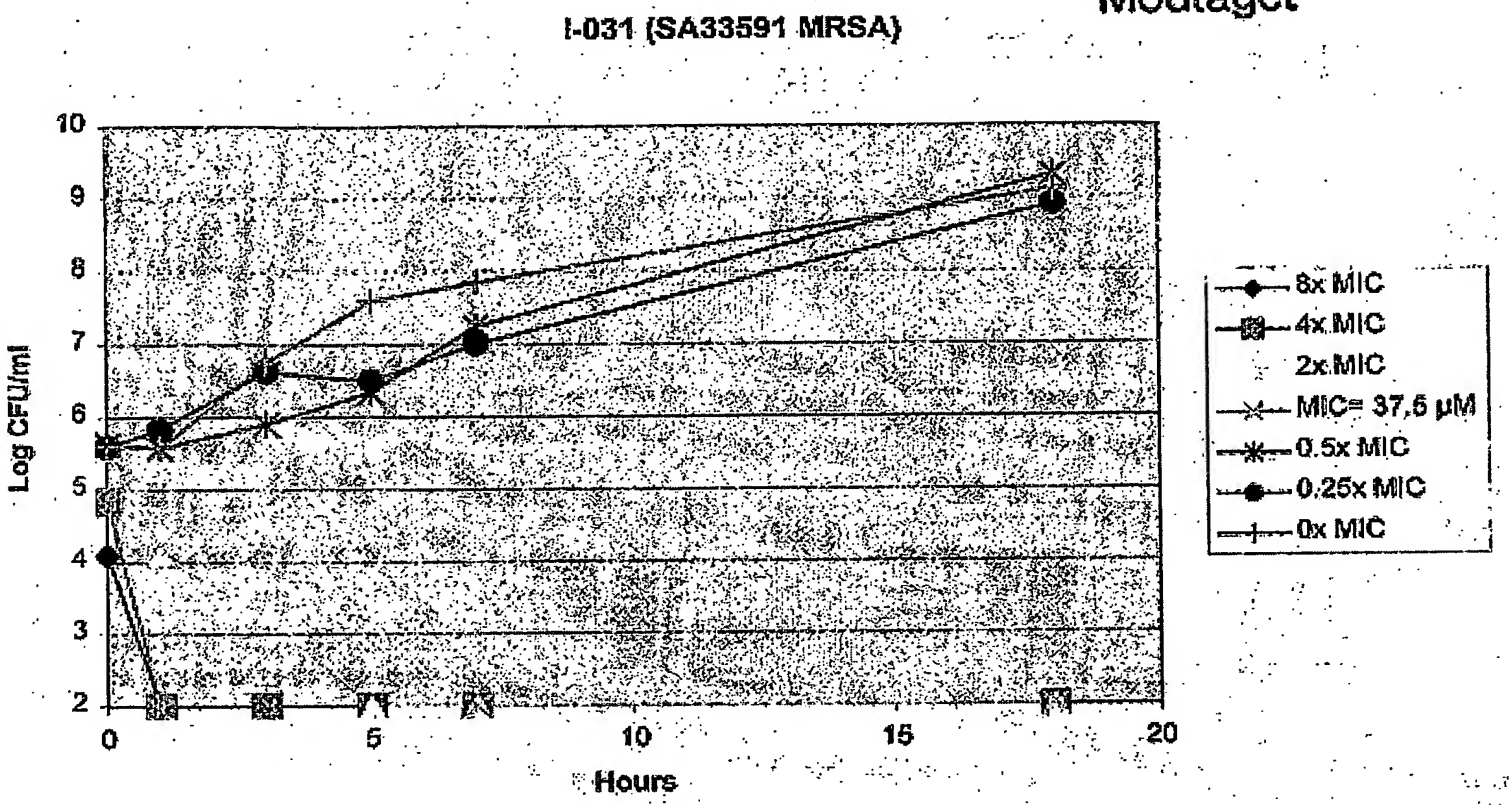


Figure 3



igure 4



igure 5

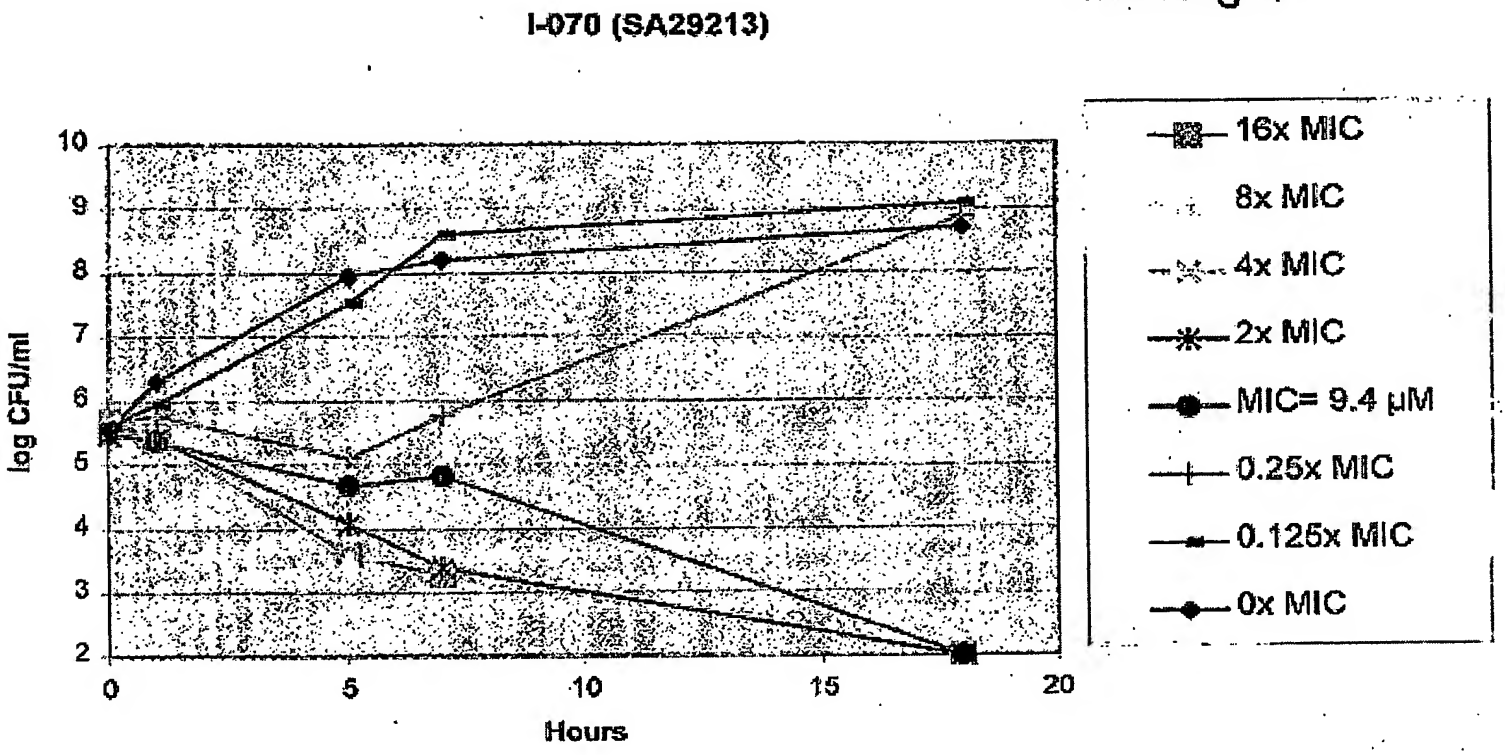
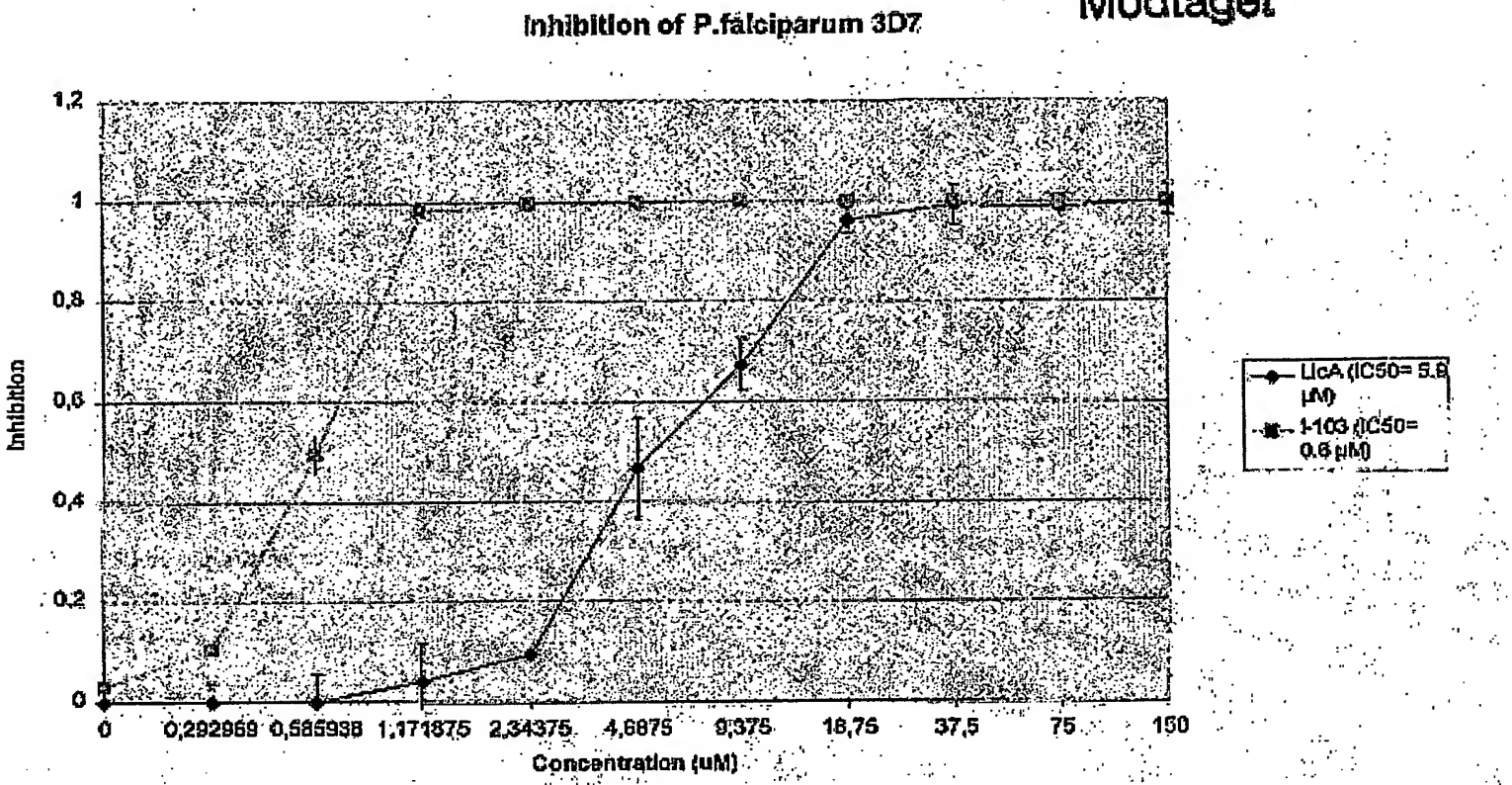


Figure 6



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